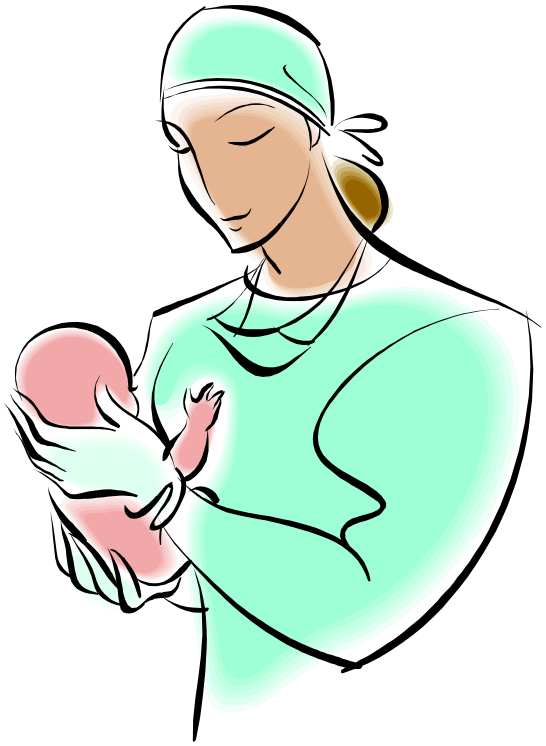
# Newborn Metabolic Screening Guidelines



*Newborn Metabolic Screening Program*

*Office of Family Health*
*Division of Health and Medical Services*
*South Dakota Department of Health*

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# Introduction

Newborn metabolic screening is an essential public health program for early identification of serious health disorders. The practice of newborn metabolic screening was originally instituted to detect phenylketonuria (PKU), but screening for additional disorders is now included in all newborn metabolic screening programs in the nation.

The goal of the South Dakota Newborn Metabolic Screening Program (SDNMSP) is to identify infants at risk for certain metabolic disorders and thereby assist with well-timed diagnosis and treatment. The ability to reduce morbidity and mortality is made possible by combined efforts of all persons involved in newborn metabolic screening. The SDNMSP operates through the collaboration of physicians, nurses and laboratory staff across the state. The State's program staff work closely with a consulting pediatric metabolic specialist and other Department staff to ensure follow-up and allow for appropriate treatment of newborns in the state.

This manual was developed to serve as a concise resource for physicians, nurses, and laboratory personnel involved in ordering newborn screening, collecting specimens, processing and reporting results of the specimens, and providing care for infants during the screening and confirmatory testing process.

# Overview

The first section of this manual consists of information on proper screening practices, including the responsibility for screening, timing of screening, and other special considerations.

Individual sections are also included for each of the three disorders for which newborn screening is mandated in South Dakota. These sections provide an overview of the condition, lab tests used for screening, categories of possible abnormal values, and discussion of the recommended follow-up and treatment for each type of abnormal result. In addition, information about "optional" supplemental screening is included.

# Mandated Newborn Metabolic Screening

The South Dakota Department of Health is vested with the authority under SDCL 34-24-17 through 34-24-24 to screen all infants born in the state of South Dakota for the identification of newborns with metabolic disorders. A copy of the South Dakota laws and administrative rules pertaining to newborn screening can be found in the appendices of this manual.

Screening includes testing for the detection of excessive phenylalanine in the blood, (phenylketonuria), hypothyroidism, and elevated blood galactose levels (galactosemia). Once identified, these newborns can receive proper treatment and counseling can be offered to the parents.

## Parents' Refusal to Have the Baby Tested

According to SDCL 34-24-17 & Admin. Rule 44:19:02:05, all infants born in the state of South Dakota must be screened for metabolic disorders. Any physician/provider caring for an infant whose parent or guardian refuses to have their infant screened must ensure that the South Dakota Department of Health Newborn Metabolic Screening Program has been notified. *This must be done within 24 hours from the time the infant is discharged from the hospital by calling* Monday through Friday at 1-800-738-2301 between 8:00-5:00 or first thing Monday morning if the infant is discharged on the weekend.

# Specimen Collection

## Responsibilities for Newborn Metabolic Specimen Collection

According to SDCL and applicable Administrative Rules Article 44:19:03:01 through 44:19:03:02.

### For births within a hospital setting:

- The attending physician, other health professional, or hospital must inform the parents, guardian, or custodian of each infant of the responsibility to have the newborn screening tests done. (Admin. Rule 44:19:02:05)

- A filter paper specimen must be collected from each newborn infant **as close to time of discharge as possible** by the institution or hospital where initial newborn care was provided regardless of feeding history. (Admin. Rule 44:19:03:02(1) Failure to collect a specimen as mandated is contrary to state law.

- For specimen collection when circumstances involve infant transfer to another facility, see "Inter-Hospital Transfer" in the "Special Considerations" section.

- If a parent, guardian, or custodian refuses consent for newborn screening to be completed for any infant, the attending physician, other health professional, hospital, or public health facility must notify the department by telephone at (605) 773-3737 or call 1-800-738-2301 Monday through Friday 8:00am-5:00pm CT within 24 hours after the refusal. (Admin. Rule 44:19:02:05)

### For births NOT within a hospital setting:

- If a birth attendant was present for the birth, the birth attendant is responsible for informing the parent or guardian of the necessity to have newborn metabolic screening done and where it can be completed. (Admin. Rule 44:19:02:05)

- If a birth attendant was not present for the birth, the local county birth registrar must inform the parent or guardian of the need for the blood test during the process of applying for a certificate of birth. The registrar must inform the parent or guardian where the blood sample may be drawn or refer them to the Community Health Nurse in that county. (Admin. Rule 44:19:03:02)

## Collection of Newborn Screening Specimens in a Clinic Setting

<u>*Initial*</u> newborn screening specimens may need to be collected in a clinic setting for infants born at home or for infants that did not have it performed during birth admission (e.g., the facility of birth inadvertently did not collect it).

The American Academy of Pediatrics (AAP) states that healthcare providers need to be aware of infants at risk of not having had a newborn screen (such as those born at home or missed during the birth admission), and states the practitioner should obtain a specimen from those infants during *their first contact with the provider.*[1]

### When collecting any specimen in a clinic setting:

Confirm **exactly** which tests are needed.
**Determine if this is the first specimen**. If so, all mandated tests must be ordered. Parents often will indicate the need for "PKU" testing, but are using this term to refer to the entire newborn screen. Remind them that PKU is only one of the tests in the newborn metabolic screen mandated by South Dakota statute, and confirm whether the other disorders have been screened for previously.

**If in doubt,** (you do not have documentation of any screening results), call the State's designated screening laboratory (CLM) at 605-328-5464 or 1-800-522-2561 or the SDNMSP at 605-773-3737. Staff can confirm with you if any tests have been performed.

*Repeat* specimens collected in clinics are not uncommon. Some of the reasons are:

- Early hospital discharge – If the initial specimen was collected within 24 hours of birth, a second specimen should be collected within 2 weeks of age.
- The initial specimen result was abnormal or indeterminate, and further testing is necessary to determine if the infant may be affected by the disorder.
- The initial specimen could not be analyzed due to improper collection or handling (quantity of blood too small to analyze, blood contaminated with other substances, blood drawn from a line through which parenteral nutrition was given, etc.).

*Confirmatory* specimens are occasionally collected in clinics. These are *NOT* collected on filter paper.

For *confirmatory* specimens, follow the instructions on the laboratory report requesting the specimen. If you need additional information or have any questions about proper collection or shipping, refer to the "Confirmatory Specimen Collection Requirements" of this manual. You may also call the State's screening laboratory (CLM) at 1-800-522-2561 or 605-328-5464.

Explain to the family your facility's notification process regarding screening results.

### Collection Requirements for Filter Paper Specimen

1. A filter paper specimen must be collected from each newborn infant **as close to time of hospital discharge as possible** by the institution or hospital where initial newborn care was provided, regardless of feeding history;
2. It is highly recommended that newborns discharged prior to 24 hours of age have a repeat specimen obtained within two weeks of age;
3. Filter paper specimens must be obtained from **premature newborns** on day of discharge or the seventh day of age if nursery stay is prolonged beyond six days;
4. Filter paper specimens must be obtained from newborns **PRIOR to any transfusions** for valid test results. Even small transfusions provide donor red

blood cells containing normal enzymes that may invalidate galactosemia and hemoglobin screening results. Likewise, transfusions may alter screening for hypothyroidism and PKU. The appropriate strategy is to always collect a newborn screening sample immediately before any transfusions, *regardless of the infant's age*. If the pre-transfusion specimen was collected before 24 hours of age, a repeat specimen must be obtained at the time of discharge. Always indicate on the laboratory requisition the **date of the most recent transfusion**.

5. If the infant was **not screened prior to transfusion**, a specimen should be collected *before discharge or within 7 days of* age. Since red blood cells and plasma transfusions can cause false negative results, post-transfusion follow-up at the appropriate time is essential. Always indicate on the laboratory requisition the **date of the most recent transfusion**. A second specimen must be collected if the first specimen does not meet the following criteria:
    - Congenital hypothyroidism: collect speciment 48 hours after the last transfusion.
    - PKU: collect specimen 48 hours after the last transfusion; assuming the infant is eating, test results should "normalize" within 48 hours time in all but the most extreme transfusion settings.
    - Galactosemia: collect specimen at time of discharge, and recommend another specimen three (3) months after the last blood transfusion. If galactosemia is a clinical consideration, dietary restriction of galactose should be maintained until an accurate test has been obtained.
6. Inter-Hospital Transfer: Infants born in South Dakota must have testing performed in South Dakota. If an infant is transferred to another hospital **before** 48 hours of age, the receiving hospital must collect a specimen at an appropriate time within the first 48 hours of life. If an infant is transferred to another hospital **after** 48 hours of age, the transferring hospital must collect a specimen before the transfer and within the first 48 hours of age. When an infant born in South Dakota is transferred out of state, the specimen needs to be submitted to the SD designated laboratory for testing.

## Confirmatory Specimen Collection Requirements

| | Specimen Collected | Tube Top Color | Comments |
|---|---|---|---|
| Congenital Hypothyroidism | Serum | Red | Pack with a "cool pack" in a box |
| Galactosemia | Heparinized whole blood and 2 blood spots | Green | Room temperature |
| PKU | Spots or Heparinized Plasma | Green (For heparinized plasma) | Frozen |

## Timing of Specimen Collection

The AAP states that the optimal time for specimen collection from a healthy newborn is as close to discharge as possible. **The American Academy of Pediatrics recommends that all infants tested before 24 hours of age should be retested before two weeks of age to avoid missing disorders.**[4]

The AAP further recommends, "A blood specimen should be obtained from every neonate before the baby is discharged or transferred from the nursery, regardless of the nature or status of the infant's feeding or age…. Any premature infant, any infant receiving parenteral feeding, or any neonate being treated for illness should have a specimen obtained for screening at or near the seventh day of age if a specimen has not been obtained before that time, regardless of feeding status". [3]

Data suggests that missed PKU cases depends on the infant's age at testing and the cutoff used. With a cutoff of 4 mg/dL, approximately 33% of infants with PKU would be missed if the sample is collected in the first 12 hours of life; 10% would be theoretically missed at 24 hours, 2.4% at 24-48 hours, and 0.15% after 48 hours. However, these are only statistical estimates of the frequency of false-negative/missed cases.[4] .

All infants screened before 24 hours of age should be rescreened before 2 weeks of age.

It is the standard of care that the screening be completed before discharge. In classic galactosemia, symptoms occur within the first 2 weeks of life: jaundice, vomiting, lethargy, hepatospenomegaly, cataracts, and failure to thrive which may proceed to death and severe morbidity from liver failure, sepsis, or bleeding if untreated.[4]

## Specimen Collection by Heelstick

**Supplies**: Filter paper blood collection card, CLM SDNMSP requisition, printed instructions for proper use of the supplies, and a preaddressed return envelope.

- **Correctly complete all information requested** on the requisition, indicating which SDNMSP mandated tests are to be performed.
- Attach a requisition identification number (at lower right corner of test requisition) to the filter paper in the area designated "Place Requisition Sticker Here." This identification number is also needed on the birth certificate certified worksheet.
- To prevent specimen contamination, do not touch any part of the filter paper circles before, during, or after collection -- with gloved or ungloved hands. Do not allow the filter paper to come into contact with substances such as alcohol, formula, water, powder, antiseptic solutions, or lotion.
- Wash hands vigorously. Wear powder-free gloves and change gloves between infants.
- Confirm identity of infant, and then *LEGIBLY* write infant's name on the filter paper card using a blue or black ball point pen only.
- Collect the blood onto the labeled filter paper using the following protocol:

## Sampling Technique

1. Place infant's limb lower than the level of the heart to increase blood flow to the foot.
2. Warm the heel. A warm moist towel at a temperature no greater than 42°C may be used to cover the site for 3 minutes; this technique increases the blood flow sufficiently without burning the skin.

3. Cleanse infant's heel with 70% isopropyl alcohol (use only rubbing alcohol). Allow heel to **air dry**.
4. Using a sterile, disposable lancet (or a disposable automated heelstick lancet device), perform a swift clean puncture on the *plantar* surface of the heel. The puncture should be made to a depth of less than 2.0 mm with the sterile lancet.
5. Gently wipe off first drop of blood with sterile gauze or cotton ball. The initial drop contains tissue fluids that may dilute the sample.
6. Allow another LARGE blood drop to form. Apply gentle pressure with thumb and ease intermittently as drop of blood forms.
7. Gently touch the printed side of the filter paper card to the blood drop and fill each printed circle, *in one step*, with a SINGLE application of blood sufficient in quantity to soak completely through the filter paper.
8. Apply blood to only one side of the filter paper. Avoid "milking" or squeezing the puncture.
9. **Do not** apply successive drops of blood (layering) to the same printed circle; if blood flow diminishes so that a circle is not completely filled, repeat sampling technique in a new circle.
10. Observe the saturation of each printed circle as the blood flows through the filter paper. Spotting should be done only on the printed side. The filter paper must not touch the skin puncture site.
11. Repeat this process to fill all required circles with blood.
12. For optional screening tests, additional spots are required.
13. After blood have been collected, elevate the infant's foot above the body, and apply pressure using sterile gauze or cotton swab pressed against the puncture site until the bleeding stops. Do not apply adhesive bandages.
14. All used items should be disposed of in an appropriate biohazard container.

*These instructions are consistent with the recommendations in *Blood Collection on Filter Paper for Neonatal Screening Programs.* National Committee for Clinical Laboratory Standards. Vol. 12 No. 13 1992 [NCCLS Document LA4-A2][2]

A full-color chart illustrating proper specimen collection, "Neonatal Screening Blood Specimen Collection and Handling Procedure," may be obtained at no charge from Schleicher & Schuell, Inc., P.O. Box 2012, Keene, NH 03431; 1-800-437-7003; FAX 603-357-7700.

## Completing the SDNMSP Laboratory Testing Requisition

**It is extremely important that all requested information on the laboratory requisition is filled out completely and legibly**. The lab requisition is a legal record; therefore, the submitter is legally responsible for the accuracy and completion of all information. All information requested is vitally important for the process of screening and follow-up. If key information is missing or unreadable, these specimens are difficult and time consuming to perform follow-up service. This may result in unnecessary delays in treating affected infants.

Rapid follow-up of an abnormal screening test depends upon identifying the physician who is caring for the child. The responsibility for follow-up of an abnormal result rests with the physician of record, as identified on the lab requisition. For these reasons, every effort should be made to ensure that this physician information is accurate and complete.

The time of collection and the medical information on transfusions, medications, prematurity, and other requested data are needed by the screening laboratory to interpret test results and determine appropriate follow-up procedures.

The Institute of Metabolic Disease at Baylor University Medical Center (the reference laboratory performing SuppNBS testing) **requires a signed consent form by the parent/legal guardian PRIOR to performing** SuppNBS. The purpose of this policy, required by Risk Management at Baylor, is to inform the parent or legal guardian of the limitations and risks associated with newborn screening – constituting an "informed consent."

To meet these requirements, the approved Baylor consent form is included on the updated newborn Screening Requisition. When SuppNBS is ordered, **the consent form on the requisition must be signed and accompany the specimen sent to CLM.**

The South Dakota Department of Health has implemented the Electronic Vital Record Screening System (EVRSS). The EVRSS establishes a direct link between the birth certificate and newborn metabolic screening, which utilizes a unique identifier number.

CLM also provides two systems of computer interface between a health care facility and their laboratory, ClinScan and NDR systems, for submitting CLM requisitions. On either of these systems, each time a newborn screening request is entered, the computer prompts the operator to enter the same required information as that requested on the "paper" Newborn Metabolic Screening requisition. The computer generates the requisition with a unique identification number (a nine character alpha/numeric field) and bar code labels for specimen identification. Hospital medical records personnel who complete the Birth Certificate Worksheet either need to write in this unique identifier or apply one of the peel off labels.

## Instructions for Completing Laboratory Requisition

| | |
|---|---|
| Physician | Full name of primary/ordering physician on the requisition. The physician named will be contacted with abnormal test results and when a specimen is unacceptable. |
| Time of Collection | State time specimen was collected using military time. |
| Mother's Name | Be sure to include the mother's **Maiden** (birth) name along with the **Last** and **First** name. The mother's Maiden (birth) name is a key component used by the SDNMSP to match birth certificates with neonatal screening test results. |
| Mother's Address | The **complete** mailing address, including street address, city, state, and zip is needed. |
| Facility of Birth | The **name** of the facility where infant was born **and** the **time** of specimen collection. |
| 1st Specimen | Mark if this is the first specimen collected for testing or if original specimen was unacceptable. |
| 2nd Specimen | Mark if this is the second specimen (test results are available from infant's first specimen.) |
| Repeat /Other | Mark if a new specimen is being submitted and indicate why. |
| Date of 1st Feeding & Type of Feeding at Discharge | Record date of first feeding (MM/DD/YY) or mark NPO or TPN if infant has not had first feeding at time of specimen collection. Indicate type of feeding at discharge: ____Breast ____Formula ___Both (check one) |
| Premature | Mark the appropriate answer. (yes or no) |
| Baby's Age | Record baby's age at time of specimen collection by marking one of the two options. |
| Was Baby Transfused Prior to Specimen Collection | Indicate yes or no. If yes, include date of last transfusion. |
| Birth Weight | Record baby's birth weight in pounds (LBS) and ounces (OZ). |
| Test(s) Requested | Mark the test(s) to be performed on the filter paper specimen. |
| Optional Tests | Mark if optional testing for Supplemental Newborn Screening (includes MCAD), Hemoglobinopathy Screen, and/or Neonatal TSH Screen is to be performed. At least *one additional* filter paper spot must be submitted for Supplemental Newborn Screening, and *two additional* filter paper spots must be submitted for Hemoglobinopathy Screening. A signed consent form must accompany the requisition for supplemental screening. Signature must be obtained **prior** to test collection. Witness should be a "non-interested" party. Possible examples are: hospital staff or a prenatal instructor. |

## Handling and Shipping the Collected Specimen

1. AIR DRY blood specimen thoroughly at room temperature for a **minimum of 3 hours**.
2. Keep specimens away from direct heat or sunlight.
3. Dry in a horizontally-level position on a non-absorbent open surface, such as a plastic test tube rack.
4. Do not stack, heat, or allow to touch other surfaces during the drying process.
5. Do not refrigerate specimen.
6. Do not place specimen in envelope until completely dry.
7. Double-check that the patient information on the laboratory requisition has been completely filled out before mailing.
8. Within **24 hours of collection**, place the requisition AND dried filter paper in the mailing envelope provided.
9. Place **each infant** screen in a **separate envelope** and seal. Do not use plastic or plasticene envelopes. Humidity and moisture are detrimental to stability of dried blood spot specimens and can affect results.
10. Double-check that a return address is present on the specimen envelope.
11. Send specimen by courier (if available) or mail directly to the laboratory. The specimen should be received at the Central Laboratory for CLM no later than 3 days after collection. Some delays are unavoidable, such as holidays. Every effort must be made to avoid delays in forwarding the samples promptly. Specimens collected on Sunday or Monday holidays are best stored in a cool room and sent express mail at the first opportunity.
12. Do not transport in plastic bags. (They allow accumulation of condensation and can contribute to contamination, elution, and bleeding of the blood spots.)
13. Assure prompt delivery to the screening laboratory.
14. Do not accumulate specimens, as they may become too old for testing.

Practitioners are encouraged to have systems in place to log and track specimens by name and unique identifying number (requisition number), to assist with follow-up in the event of an abnormal newborn screening test result.

## Report of Results

Newborn screening results may be negative (no evidence of the disorder), positive (evidence of disorder), indeterminate, or unsatisfactory.

- **Negative/Normal results** will be reported daily to the submitter and the SDNMSP.

- **Positive/Abnormal results** will be reported to the submitter, the physician named on the test requisition and the SDNMSP no later than 24 hours after analysis by facsimile and/or telephone.

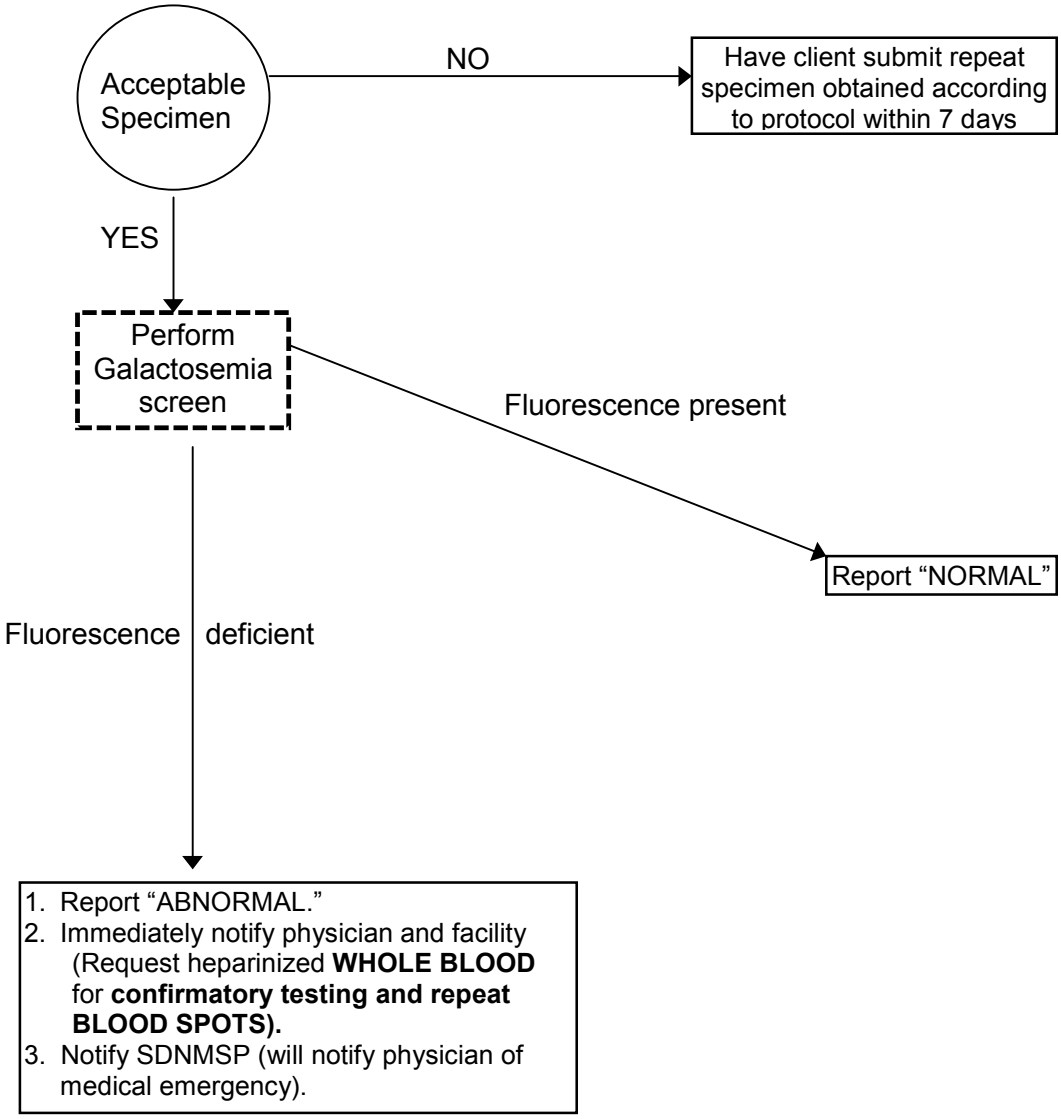
- **Indeterminate results** will be reported to the submitter, the physician named on the test requisition and the SDNMSP no later than 24 hours after analysis by facsimile and/or telephone.

- **Unsatisfactory specimens** will be reported to the submitter by telephone and facsimile with reason for specimen rejection and the need for a repeat specimen. (See "Criteria for Acceptable and Unacceptable Neonatal Specimens" (page 6).

We encourage all providers to ascertain the results of newborn screening on any infant in their care. Do not presume that a newborn screening test was obtained, or that the results of the newborn screen were normal.

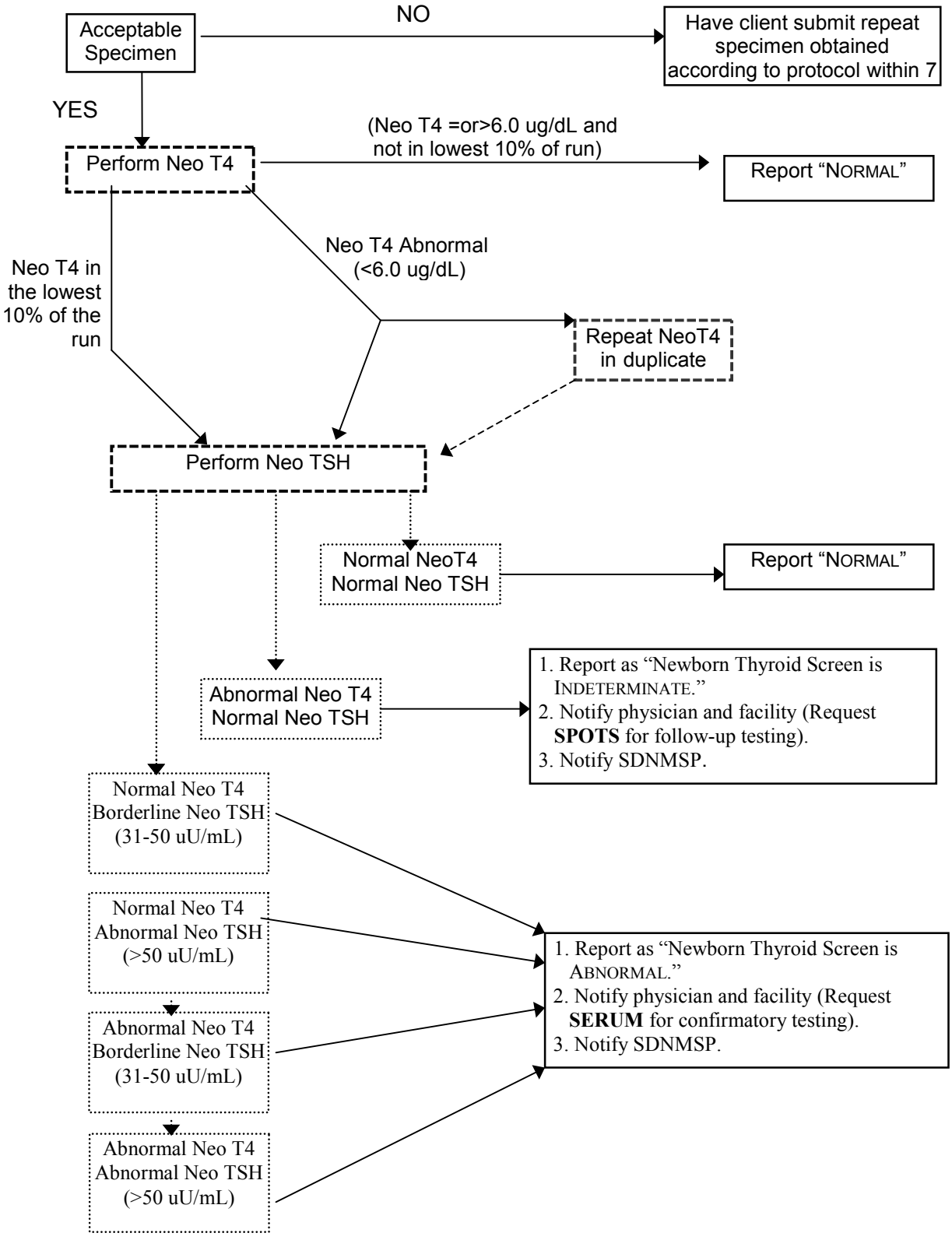
# Galactosemia – Collection and Reporting Flowchart

Updated 03-02



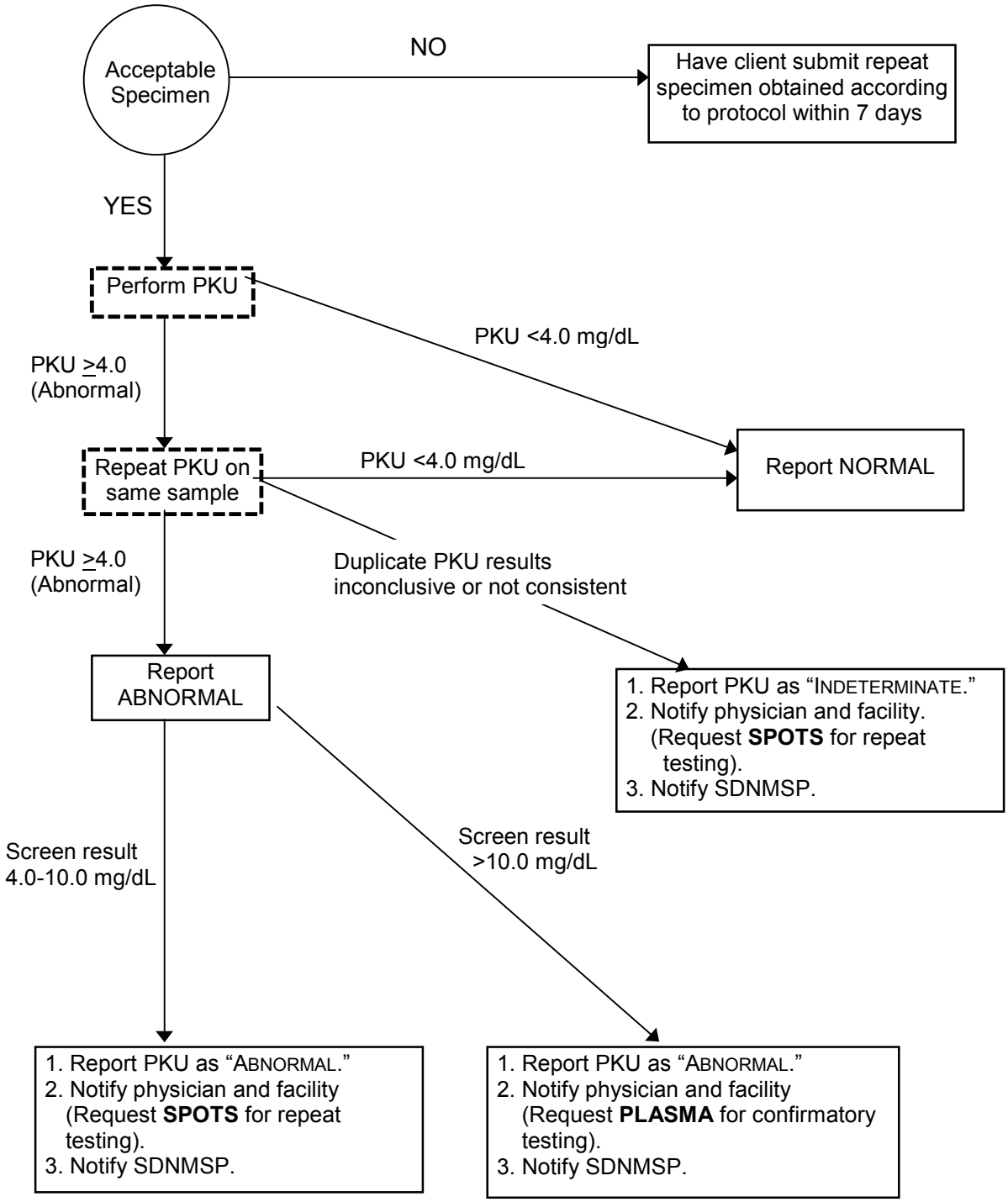
# Neonatal T4 – Collection and Reporting Flowchart

Updated 03-02



# PKU – Collection and Reporting Flowchart

Updated 03-02



## Criteria for Acceptable and Unacceptable Specimens

If CLM receives a specimen that is determined to be unacceptable or unsatisfactory, proper protocol will be followed to request a new specimen. Unacceptable specimens adversely affect turnaround time and potentially delay the testing and screening of an affected infant. Since an unacceptable specimen gives no usable information, it is necessary to determine the acceptability of the specimen as soon as possible so that an acceptable specimen can be obtained. Follow the guidelines below to determine acceptability of specimens submitted:

**Acceptable:**

- A sufficient quantity of blood soaked through to fill a preprinted circle on the filter paper completely.
- Blood applied to only one side of the filter paper.
- Specimen properly dried before being placed in mailing envelope.
- Specimen transported in a paper envelope, optimally within 24 hours of collection.
- Sufficient number of circles completely filled for testing ordered.

**Unacceptable:**

- Tissue fluid or serum has separated from the blood, evidence of milking or squeezing the puncture.
- Layering of successive drops of blood in the same printed circle.
- Insufficient quantity of circles filled completely for testing ordered.
- Blood clots are present on the specimen.
- Blood fixed by heat or age will not elute from the blotter paper.
- Evidence the specimen was smeared or touched during drying.
- Specimen subjected to extreme temperatures, especially heat during the summer.
- Evidence that the circle was contaminated with water, feeding formulas, antiseptic solutions, powder from gloves, etc. before or after the collection.
- Insufficient drying of specimen before shipment.
- Filter paper cards from several newborns stacked together without a paper separator, possibly causing cross-contamination.
- A small percentage of smaples submitted to the laboratory contain insufficient blood (Quantity Not Sufficient" or "QNS") for analysis.
- Cord blood is NOT adequate for detection of PKU or other disorders with metabolite accumulation after birth. [4-re9243]

# Special Considerations

Situations such as those outlined below may increase the risk of a false negative or false positive screening test result.

## Blood Transfusions

A specimen should always be taken **before a blood transfusion**, regardless of the infant's age. Donor blood provides red blood cells, which contain normal enzymes that may alter the galactosemia assay and donor hemoglobins that will alter screening for hemoglobinopathies. Likewise, transfusions may alter screens for hypothyroidism and PKU. South Dakota Newborn Metabolic Screening regulations require that a specimen is obtained from newborns undergoing a transfusion **prior to the transfusion** and a repeat specimen must be obtained at the time of discharge.

If the infant was **not screened prior to transfusion**, a specimen must be collected *prior to discharge or within 7 days of age*. Always indicate on the laboratory requisition the **date of the most recent transfusion**. A second specimen must be collected if the first specimen does not meet the following criteria:

- Congenital hypothyroidism: collect specimen 48 hours after the last transfusion.
- PKU: collect specimen 48 hours after the last transfusion; assuming the infant is eating, test results should "normalize" within 48 hours time in all but the most extreme transfusion settings.
- Galactosemia: collect specimen at time of discharge, and recommend another specimen three (3) months after the last red blood cell transfusion. If galactosemia is a clinical consideration, dietary restriction of galactose should be maintained until an accurate test has been obtained.

**Practitioners must therefore remain alert to clinical symptoms in older infants despite normal initial screening.**

## Premature or Sick Infants (Prolonged Hospitalization)

South Dakota regulations state that specimens must be obtained from premature or sick newborns on the day of discharge or on the seventh day of age if nursery stay is prolonged beyond six days. (Admin. Rule 44:19:03:02)

It is important to remember that T4 results may be quite low in normal premature infants. Therefore, a low T4 should always be monitored closely to assure that T4 levels rise into the normal range as the infant matures.

As noted above, always obtain the newborn screening specimen **prior to a blood transfusion**, regardless of the infant's age. Refer to the Blood Transfusions section, under Special Considerations above, for details regarding screening guidelines.

## Dietary Intake and Screening

Practitioners need to be aware that a specimen collected prior to 24 hours of age will usually detect galactosemia, but will be less reliable for other disorders. The trend toward early discharge from the nursery complicates newborn screening. In certain metabolic conditions such as PKU, the accumulation of the specific amino acid(s) in the blood does not occur until after birth, when the intake or production rate exceeds the affected infant's capacit to metabolize or excrete it.

The phenylalanine level of affected infants rises gradually after birth with little, if any, effect of the amount of protein ingested by the infant. The infant must be at least 24 hours of age to reliably detect PKU. Those with milder forms of hyperphenylalanemia may need to be older to develop abnormal test results.

## Hyperalimentation and Antibiotic Therapy

These are not contraindications to testing, but the specimen for screening should never be taken from the intravenous line, that is used to deliver the alimentation or drugs. High serum levels of several amino acids can occur during hyperalimentation. Be sure to specify "TPN" on the lab requisition to assist the screening laboratory in interpreting the results. Antibiotic therapy does not interfere with testing methods used by the SDNMSP.

## Inter-Hospital Transfer

Special care needs to be taken to ensure that infants who are transferred between hospitals have been screened for metabolic disorders. Infants born in South Dakota must have testing performed in South Dakota. For infants born in South Dakota and transferred out of state, the specimen needs to be submitted to the South Dakota designated laboratory for testing.

### According to South Dakota regulations:

- If an infant is transferred to another hospital **before** 48 hours of age, the receiving hospital must collect a specimen at an appropriate time within the first 48 hours of life. (Admin. Rule 44:19:03:02)
- If an infant is transferred to another hospital **after** 48 hours of age, the transferring hospital must collect a specimen before transfer within the first 48 hours of life. (Admin. Rule 44:19:03:02). When an infant born in South Dakota is transferred out of state, the specimen needs to be submitted to the SD designated laboratory for testing.

The American Academy of Pediatrics recommends that the first hospital must inform the second hospital when an initial, repeat, or confirmatory specimen is needed.[3] The SDNMSP recommends that this information be easily located on any transfer form. In this way, both sending and receiving hospitals are responsible to verify that newborn metabolic screening has been completed. If a physician is no longer caring for or cannot locate the infant, he or she should notify the SD Newborn Metabolic Screening Program at (605) 773-3737.[1]

## Challenges in Newborn Metabolic Screening

Newborn screening can be complicated by many factors, including, an infant's illness or prematurity, blood transfusions, out-of-hospital births, and hospital transfers. Follow-up of abnormal screening results can be hampered by incomplete or inaccurate patient or physician information on the lab requisition, name changes, unsatisfactory specimen collection, and so on.

## Infants Who Are Not Tested

Physicians and hospitals should ensure that:

- The infant's parents or legal guardian have been informed of the need for metabolic screening;
- the newborn screening tests have been performed; and
- the test results were completed.

## Common Misconceptions

Some people believe the tests are not accurate if the infant is tested before 24 hours of age. It is the standard of care to obtain newborn screening before discharge from the hospital regardless of infant's age or feeding history. However**, if the initial specimen for newborn screening is collected before 24 hours of age, a second specimen should collected before 2 weeks of age,** according to AAP recommendations.

# Clinical Signs or Family History

There are a number of clinical situations that will modify the usual approach of obtaining a newborn screening specimen and waiting for the result. The following are brief suggested guidelines for particular situations that may arise in clinical practice. **Regardless of any diagnostic or therapeutic interventions, a newborn screen should be obtained on all infants to test for the other conditions included in the panel.** When in doubt about the course of management for any of the conditions on the screening test, consultation with a specialist is advised.

## Newborn Screening of Infants Who Exhibit Clinical Signs and Symptoms

The newborn screening test, like any laboratory test, may have false-positives and false-negatives. If signs and symptoms of one of the newborn screen conditions are evident clinically, the physician should proceed to diagnostic testing, pending the results of the screen or in spite of the results of the screen.

- **If the results of the newborn screen are pending:**
  For any of the screened conditions, but especially those in which the metabolite accumulation is dangerous, such as galactosemia, **treat as if the infant has the condition**. For other conditions, contact a metabolic center or metabolic physician for assistance with rapid diagnosis and institution of dietary treatment; for galactosemia, begin a galactose-free and lactose-free formula until the screening results are known.
- **If the newborn screening test result was "normal":**
  If clinical symptoms suggest one of the screened conditions despite a "normal" screening test, the physician should **proceed as if the patient has the condition** and immediately contact a consultant specialist for instructions on further evaluation of the patient.

## Newborn Screening of Infants with an Affected Close Relative

As many of the conditions tested for by newborn screening are genetic, it is possible that multiple members of a family may be affected. Prenatal diagnosis is possible for many of these conditions; if prenatal diagnosis determines that the infant is affected, any appropriate treatment (e.g., special diet) should be initiated immediately after birth.

If prenatal diagnosis predicts an unaffected baby, practitioners should bear in mind that no prenatal diagnostic test is 100% accurate. Neonates who are siblings or close relatives of an affected individual are not part of the "general population" for whom newborn screening is designed. For any infant with a positive family history, providers should contact appropriate consultant specialists, ideally prenatally, or immediately at birth, to determine the proper diagnostic tests and proper timing of those tests.

# Purpose of Screening

Babies with these conditions appear normal at birth. With time, the condition can affect the baby's brain or physical development or causes other medical problems in which the damage may become permanent. Early diagnosis and treatment can reduce morbidity and mortality.[4]

The purpose of newborn metabolic screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results alone are insufficient information on which to base diagnoses or treatment.

# Education Services

On-site in-services to facilities performing newborn metabolic screening are available as needed upon request. Educational materials are available for clients and practitioners. The SDNMSP has developed a brochure explaining the need for newborn metabolic screening. Items and ordering information follows.

- Newborn Screening This pamphlet provides general information on newborn metabolic screening, and is available free of charge from the South Dakota Department of Health Resource Center by calling 605 734-4550 or sending your request via FAX to 605-734-4552. The order number for the pamphlet is MCH-001. Facilities may be charged for shipping and handling when ordering in quantity.

- SDNMSP Metabolic Screening Manual The Department of Health distributes this manual to all hospitals and clinics in the state that provide services to infants..

The most recent version of the Metabolic Screening Manual is available on the DOH, SDNMSP web site. Information and links to other sites relating to specific metabolic disorders can be found on the web site as well. See Resource page for the web site address.

# Designated Newborn Screening Laboratory

In order to conduct effective, timely follow-up for newborns affected by any of the disorders, the South Dakota Department of Health uses a centralized system to coordinate analyzing, reporting, and follow-up of newborn metabolic screens.

The Department, along with assistance from national experts, has used a request for proposal process to designate the laboratory for the Newborn Metabolic Screening Program.

Clinical Laboratories of the Midwest (CLM) is the laboratory authorized to conduct newborn screening services for the state of South Dakota. **All newborn screening specimens for infants born in South Dakota must be submitted to CLM. This includes follow-up and confirmatory specimens.**

The following numbers are provided for quick reference:

- Support Services at 605-328-5464 or 1-800-522-2561 for questions regarding specimen collection, handling and shipping.
- Supplies at 605-328-5466 or 1-800-522-2561, ext. 8-5466 to obtain additional filter paper, newborn screening brochures or other related supplies. Supplies requisitions may also be faxed to 605-328-5405.

# Phenylketonuria (PKU)

A total lack of the hepatic enzyme phenylalanine hydroxylase results in the markedly elevated blood phenylalanine concentration levels typical of phenylketonuria (PKU). The overall incidence of PKU is 1:12,000 to 1:16,000 live births, depending on the ethnic background of the population.[4] This metabolic disorder is caused by a recessively inherited enzyme defect in which the body cannot properly use the amino acid phenylalanine. All other metabolic processes are intact, but phenylalanine, which comes from all dietary protein, accumulates in the blood. Excess phenylalanine cannot be converted to tyrosine due to a lack of phenylalanine hydroxylase, the enzyme that catalyzes the conversion of phenylalanine to tyrosine. The phenylalanine and its metabolites accumulate in the body and cause damage. Most abnormalities in the metabolism of the amino acid phenylalanine are caused by mutations in the gene, which is responsible for the production of the enzyme phenylalanine hydroxylase. Phenylalanine, an essential amino acid, is normally converted to tyrosine by this enzyme, which uses tetrahydrobiopterin as a cofactor. Normal metabolism of phenylalanine results in a serum concentration between 0.5-3 mg/dL.

## Clinical Features

Classical phenylketonuria is a disorder in which the blood phenylalanine, or Phe, rises above 20 mg/dL on a normal diet. Other symptoms, including severe mental deficiency, microcephaly, eczematous or oily skin, cerebral palsy, spasticity, seizures, eczema, convulsions, dysphasia, hyperactivity with purposeless movements, autistic-like behavior, and an abnormal EEG, usually develop. Physical findings are non-diagnostic. The skin and hair are usually fair and the eyes may be blue. In addition to a marked elevation of blood phenylalanine, phenylketones may be produced when the blood level is above 20 mg/dL. These compounds have a peculiar, mousy odor in the baby's urine, sometimes noticeable in untreated patients. The smell arises from phenylacetic acid (children who are enuretic may also smell the same due to bacterial degradation of a normal, though unimportant, constituent of normal urine).

Hyperphenylalaninemia refers to any consistent elevation of Phe levels, including classical PKU. If cases of classical PKU are excluded, this includes blood Phe levels between 4-20 mg/dL. These may be caused by liver damage, transient tyrosinemia of prematurity, mutation of the phenylalanine hydroxylase gene, disorders of cofactor synthesis or regeneration, or maternal PKU. In these cases, mental retardation is variable and, in milder variants, is completely absent. Blood levels may remain high throughout life or may gradually fall toward normal. In infancy, these patients can mimic the severe PKU condition, and even in mild cases there seems to be an increased risk of the maternal PKU syndrome.

Much rarer forms of hyperphenylalaninemia are caused by defects of biopterin metabolism. Blood phenylalanine levels are variable. These patients have progressive neurological damage with seizures and steady deterioration that becomes noticeable sometime between 6 and 20 months of age despite early treatment with a low phenylalanine diet. Definitive tests can differentiate these variant forms of PKU. In view

of the severity of this group of diseases, all infants with persistently abnormal levels of phenylalanine should be tested by special blood or urine tests for biopterin abnormalities.

The cause of hyperphenylalaninemia must be determined if proper treatment is to be provided. Treatment by dietary restriction alone is inadequate for a tetrahydrobiopterin cofactor defect. The cofactor is necessary not only for normal activity of phenylalanine hydroxylase, but also for activity of the tyrosine and tryptophan hydroxylase which synthesize serotonin and dopamine.

## Maternal PKU Syndrome

Pregnancy presents a special problem with PKU and hyperphenylalaninemia, since high blood levels of phenylalanine are teratogenic to the fetus. If maternal PKU is suspected, the mother should be appropriately tested and counseled. Ideally, women with PKU should be on a medically supervised, phenylalanine-restricted diet before conception and maintain metabolic control throughout pregnancy.

This is also important in the context of newborn screening because early testing of an infant born to a mother with PKU or hyperphenylalaninemia can reflect the *mother's* phenylalanine levels. A positive test on a newborn followed by a normal repeat test, especially if the baby has growth retardation, microcephaly, or malformation, should raise the possibility of maternal PKU. These infants usually have a transient elevation of phenylalanine (4-20 mg/dL) which falls to normal within 24 hours. If maternal PKU is suspected, the mother should be appropriately tested and counseled. Treatment in future pregnancies may prevent similar effects on future offspring.

The purpose of newborn metabolic screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false-negative and false-positive results are possible. Screening test results are insufficient information on which to base diagnoses or treatment

## Laboratory Tests

There are a variety of laboratory tests used in screening for PKU. The SDNMSP lab uses the Quantase Phenylalanine assay, a colorimetric end-point method that uses the enzyme phenylalanine dehydrogenase, to catalyze the NAD-dependent oxidative deamination of phenylalanine to phenylpyruvate and ammonia. The NADH produced is measured colorimetrically. An important advantage of this method over the commonly used Guthrie method is no antibiotic interference.

Abnormal newborn screening test results must be confirmed before a specific diagnosis can be made. A quantitative plasma phenylalanine level (includes tyrosine) is performed for confirmation of screening results. A tyrosine level is important to exclude hepatic causes of hyperphenylalaninemia. Urine and serum pterins should be measured to diagnose cases of dihydropteridine reductase deficiency or a defect in tetrahydrobiopterin synthesis.

## Screening Practice Considerations

Elevated plasma phenylalanine is not detectable in cord blood. Phenylalanine levels start rising within 24 hours after birth and reach20 mg/dL or more within a few days. The screening test is often abnormal within 24 hours after birth regardless of intake, and almost uniformly abnormal within 48 hours of birth in infants with PKU. The phenylalanine level of affected infants rises gradually after birth with little, if any, effect of the amount of protein ingested by the infant. The practice of early discharge from the nursery may lead to a falsely negative screening result. An increased incidence of false positive results may occur: 1) in heterozygotes due to reduced clearance capacity, 2) in newborns of phenylketonuric mothers due to the increased maternal phenylalanine load, or 3) in premature newborns because of immature phenylalanine clearance systems. If an infant is tested "early" (less than 24 hours of age) a repeat screen is **highly recommended** within two weeks of age regardless of prior results. **It is recommended to start an affected infant on treatment by one month of age, ideally by two weeks of age.** Children who develop retardation before one year of age should undergo testing for PKU even if a negative screening test is documented.

Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screens is present. These situations can include specimen collection, prematurity, heat-damaged specimen, or hyperalimentation. The presence of any of these does **not** exclude the possibility of disease.

Contamination of the filter paper with food or liquids containing NutraSweet (Aspartame) may also cause false positive results.

## Treatment

Consultation with a pediatric metabolic specialist should be made for confirmation and diagnosis. Once diagnosis has been made, dietary restriction of phenylalanine should be initiated promptly, since delays have been correlated to increasing severity of retardation. Symptoms of classical phenylketonuria are preventable with early treatment, which should be started as soon as possible after birth, once phenylalanine elevations are confirmed and other possible causes excluded. Phenylalanine levels over 6 mg/dL should be monitored indefinitely. Dietary restriction of phenylalanine is the mainstay of therapy in most cases. Because phenylalanine is an essential amino acid, it is necessary to consume a minimal amount, which must be carefully monitored and adjusted periodically with growth. A special medical food containing amino acids (except phenylalanine), vitamins, and iron is necessary in conjunction with a carefully prescribed and monitored diet to prevent protein/calorie malnutrition, osteoporosis, and catabolism.

Late treatment of PKU is variably effective. Behavior may improve, but reversal of mental retardation does not. Discontinuation of treatment is associated with variable loss of intellectual functioning, hyperactivity, and onset of seizures and other neurological signs.

With early and proper treatment, mental retardation is normally preventable. Treatment should be started as soon after birth as possible in any infant with phenylalanine levels

over 6 mg/dL and should be continued indefinitely. Frequent monitoring is required, especially in the first weeks, because infants with variant forms of hyperphenylalaninemia may be indistinguishable from true PKU and improper nutritional therapy can be fatal. The South Dakota Newborn Metabolic Screening Program has available medical and dietary specialists trained in the management of PKU children. If treatment is not started for some weeks, the results are more variable and the I.Q. tends to be lower. Patients who are not treated until after six months may show some improvement in I.Q., although they are likely to remain retarded. Older patients usually show little change in I.Q. with treatment, but a low phenylalanine diet may help to control serious behavior problems.

## Dietary Management of PKU

The main goal of dietary management of PKU is to prevent mental retardation and other neurologic sequelae from PKU based on restriction of the dietary intake of phenylalanine while adequate protein and caloric intake is maintained. The diet is planned to provide a sufficient amount of phenylalanine and other amino acids to allow normal growth and development. In the past, people with Phenylketonuria were sometimes advised to discontinue their phenylalanine restricted diet when they were children. It was not known then that this recommendation would have any harmful affects. Recent studies have found that children with PKU who ended the diet in early childhood had impaired intellectual development, impaired social functioning, and continued neurologic deterioration into adulthood.[10] All persons with PKU should remain on a restricted diet indefinitely in order to maintain a safe level of phenylalanine and have the best health outcomes. It is especially important for women with PKU to be on the diet before and during pregnancy to prevent birth defects.

- **Diet**
  The diet consists of foods that have a restricted phenylalanine content. Mothers of infants with PKU should be encouraged to administer a diet that consists of a special phenylalanine-free metabolic formula in combination with breast milk or infant formula. Infants will gradually progress to eating all fruits and vegetables (except legumes) and other foods that are low in phenylalanine. A Phe-restricted diet should keep serum concentrations between 2-6 mg/dL, while containing enough nutrients for normal body function. High protein foods such as meat, fish, eggs, poultry, dairy products, nuts, peanut butter, legumes, soy products and aspartame in diet drinks and nonglucose sweeteners should be avoided. Eating these foods will cause high blood phenylalanine levels.[9]

- **Food List**
  Food lists containing phenylalanine (Phe) content of food have been compiled for use in following a Phe restricted diet. The use of a food list to determine Phe content is an essential component of managing PKU. Use of food labels is not sufficient, as Phe content is not listed. The protein content listed on a food label can be rounded up or down, so is inadequate for estimation of Phe. As the young child transitions to table foods, parents must continue to use the food list to identify any ingredients which are unacceptable in the diet for PKU. As the child

matures, he or she can be involved in the use of the food list as well and should become increasingly responsible for this task.

- **Metabolic Food**
  Metabolic formula, which contains protein, vitamins, minerals and calories with no phenylalanine, is taken along with a controlled diet. The protein provided by the metabolic formula is from amino acids, excluding phenylalanine. The metabolic formula allows adequate protein for growth without the harmful affects of large amounts of phenylalanine. Since phenylalanine is an essential amino acid, a small amount is needed by the person with PKU. This amount is obtained from measured amounts of allowed foods. Metabolic formula is the most important part of the diet for PKU. Another important part of the diet is low protein breads and pastas. They are nearly free of phenylalanine, allowing greater freedom in food choices, and provide energy and variety in the diet. The metabolic doctor and dietitian can carefully plan the amount of drink and food consumed in one day.

Although PKU is not preventable, its symptoms can often be treated successfully through the use of a carefully regimented diet. While phenylalanine restricted diets have proven to be highly effective in preventing mental retardation, it is now recognized that there may still be subtle cognitive deficits. Usually the individual has a normal IQ, but the incidence of attention deficit hyperactivity disorder (ADHD) and learning disabilities is higher compared to those children who do not have PKU.

# Congenital Hypothyroidism (Thyroxine)

Congenital hypothyroidism (CH) is one of the most common conditions detected by newborn metabolic screening, and represents one of the most common preventable causes of mental retardation.[3] It is caused by inadequate production of thyroid hormone, which is important for the normal functioning of all the body's organs and is essential for normal brain development. Thyroid hormones regulate the metabolic rate in the body. Near the end of the first trimester of pregnancy, T4 secretion from the thyroid gland of the fetus begins. Fetal thyroid function is independent of the mother's, since thyroid hormones are not transported through the placenta. A low T4 concentration or elevated TSH level in an infant's blood is one of the earliest laboratory indicators of congenital hypothyroidism. If this condition is not treated, hypothyroidism can cause mental retardation.

Most children with congenital hypothyroidism who are not diagnosed and treated properly have varying degrees of growth failure, irreversible mental retardation, deafness, and neurological abnormalities. The incidence of hypothyroidism is 1:3,600 live births.[4]

## Clinical Features

Deficiency of the thyroid hormone in an infant may result in mental and growth retardation if it is not diagnosed and treated early in life. Infants may appear normal at birth. The hypothyroid fetus is partially protected by placental transfer of maternal thyroid hormone. [4]

When symptoms are present, they may include prolonged neonatal jaundice, constipation, lethargy and poor muscle tone, feeding problems, a large tongue, puffy face, large fontanelle, distended abdomen, and umbilical hernias.

## Diagnosis

More than 95% of infants with sporadic hypothyroidism show such minimal signs at birth that the diagnosis is missed.[4] **Therefore, *in the newborn,* clinical signs and symptoms alone are not reliable indicators of CH.** Diagnosis of many neonates is missed at birth due to the high percentage that do not show any clinical signs or symptoms. **Laboratory test results are the only reliable means of diagnosing congenital hypothyroidism in the newborn infant.**

## Causes of Congenital Hypothyroidism

The most common causes are total or partial failure of the thyroid gland to develop (aplasia or hypoplasia), or its development in an abnormal location (an ectopic gland). Less commonly, CH is induced by medications (anti-thyroid drugs or excess iodine) in the mother, maternal autoimmune thyroid disease that is due to a hereditary inability to manufacture thyroid hormones, or pituitary insufficiency.[4]

## Laboratory Tests

The program in South Dakota employs a two-tiered approach in screening for hypothyroidism. The initial screening measures the quantity of thyroxine (T4), in the

dried filter paper blood spot, using a solid phase fluroimmunassay with specific monoclonal antibodies for T4. Abnormal T4 samples with results below the normal Neo T4 cut-off are retested in duplicate and are screened using a thyroid stimulating hormone (TSH) assay. Both tests are performed on the original filter paper sample.

In addition, the 10 percent of samples with the lowest T4 results for each T4 assay run are screened with a TSH assay, performed on the same filter paper sample, a nationally accepted quality assurance practice.

Different combinations of results are possible. If the TSH screen is borderline or abnormal, a serum sample is requested for follow-up with confirmatory Free T4 and TSH testing. (Refer to "Neonatal T4" Flow Chart )

**Neo T4:**
Normal - 6 ug/dL or greater
Low - Less than 6 ug/dL

**Neo TSH:**
Normal - Less than 30 uU/mL
Borderline - 31-50 - uU/mL
Abnormal – Greater than 50 uU/mL

| Abnormal Result | Likely Causes | Recommended Follow-up |
|---|---|---|
| TSH elevated<br>T4 low or normal | ▪ Hypothyroidism<br>▪ False positive | Immediate serum thyroid testing |
| TSH slightly elevated ("borderline")<br>T4 low or normal | ▪ Hypothyroidism<br>▪ Early collection of specimen (< 24 hours)<br>▪ False positive | Second newborn screening test |
| T4 low/TSH normal | ▪ Early collection of specimen(< 24 hours)<br>▪ Thyroid Binding Globulin (TBG) deficiency.<br>▪ False positive result<br>▪ Pituitary gland problems with secondary hypothyroidism<br>▪ Prematurity (see below) | Second newborn screening test |

The AAP guidelines offer the following basic recommendation for follow-up of an abnormal newborn screening test result for hypothyroidism:

Any infant with a low T4 level and TSH concentration greater than 40 mU/L is considered to have primary hypothyroidism until proved otherwise. Such infants should be examined immediately and have confirmatory serum tests done to verify the diagnosis. Treatment with replacement l-thyroxine should be initiated before the results of the confirmatory tests are available. In cases in which the screening TSH concentration is only slightly elevated but less than 40 mU/L, another filter paper specimen should be obtained for a subsequent screening test.[3]

## Screening Practice Considerations

Congenital hypothyroidism is the most common disorder detected by the program. Detection does not depend on nutritional factors. The majority of hypothyroid infants are detected on the first specimen even if it is collected within a few hours after birth.[4] As is true with other conditions, a blood transfusion may alter the values; **the newborn screening specimen should always be collected prior to a blood transfusion, regardless of the infant's age or timing of transfusion.**

The normal newborn demonstrates a TSH surge in the first hours of life as an adaptation to the extra-uterine environment. To be valid, a specimen should be collected as close to time of hospital discharge as possible, but no later than 7 days of age. In the most recent policy statement for newborn screening guidelines for congenital hypothyroidism, the American Academy of Pediatrics recommends that every infant should be tested before discharge from the newborn nursery.[3] If the specimen is collected less than 24 hours after birth**, repeat testing is highly recommended** at two weeks of age. A small percentage of cases of congenital hypothyroidism do not develop until after the first weeks of life. Therefore, as with other screening tests, in the presence of clinical symptoms evaluation for congenital hypothyroidism should be performed despite normal newborn screening results.

Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screens is present. These situations can include early specimen collection and prematurity. The presence of any of these does **not** exclude the possibility of disease.

## Thyroid Function in Premature Infants

In premature infants, there appears to be a physiological reduction in blood T4 levels. This is not due to a low thyroid binding globulin (TBG) and the TSH levels are not usually elevated. These cases need special observation and follow-up to ensure that the low T4 levels rise into the normal range as the infant matures, but this may take several weeks.

## Treatment

Consultation with a pediatric endocrinologist should be made for confirmation and diagnosis. Treatment of congenital hypothyroidism is simple and effective. Thyroid hormone (Synthroid or Levothroid), in pill form is crushed, mixed with water, breast milk, or formula and administered once daily beginning within the first few weeks of life.[3] (Generic forms of levothyroxine sodium should **never** be used to treat hypothyroidism.)

Infants should be seen on a regular basis for an exam and have blood tests to check T4 and TSH levels to ensure that the dose of medication is adequate. As infants grow, the dose of thyroxine is increased. Infants should also undergo periodic developmental testing. Refer to the American Academy of Pediatrics *Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines* for further information.

# Galactosemia

Galactosemia is an autosomal recessive inherited metabolic disorder. The metabolic defect results in abnormal galactose metabolism caused by the deficiency of any of the three enzymes of the galactose catabolic pathway: galactose-1-phosphate uridyl transferase (Gal-1-PUT), galactokinase, or UDP-galactose 4 epimerase. Clinically, deficiency of galactose-1-phosphate uridyl transferase (Gal-1-PUT) has become synonymous with classical galactosemia.

Galactose is a component of lactose, the principle carbohydrate of mammalian milks and most non-soy commercial infant formulas. Lactose is hydrolyzed to glucose and galactose in the intestine. The body cannot break down the galactose without the proper enzymes. The galactose builds up in the body and causes cellular damage and even death. The incidence of galactosemia is estimated at 1:60,000 - 80,000 births per year.[4]

## Clinical Features

The severe form of this disease is due to almost total deficiency of galactose-1-phosphate uridyl transferase enzyme activity in all cells of the body. The early clinical features of severe galactosemia include liver dysfunction manifested as jaundice and hypoglycemia; neurological findings of irritability and seizures; and gastrointestinal finding of poor feeding, failure to thrive, vomiting and diarrhea. Death may result from gram-negative sepsis within one to two weeks of birth.[4] If the infant is untreated and survives the neonatal period, cataracts, cirrhosis, Fanconi's syndrome, and mental retardation are usual developments.

There are several genetic variants with less severe reduction in the enzyme activity (e.g., the Duarte variant). Most of these cases are asymptomatic and are detected because of a persisting abnormality in the enzyme test. However, some of these cases may require dietary therapy if galactose-1-phosphate accumulates. For this reason many of these infants require further testing, and should be evaluated by a pediatric specialist.

Deficiency of galactokinase is a rare defect associated with the development of cataracts in infancy and possibly with some degree of mental retardation.

## Laboratory Tests

The South Dakota Newborn Metabolic Screening Program uses the Beutler enzyme assay that depends upon fluorescence produced by the normal enzyme cascade in red blood cells. Dried blood spots are incubated with galactose-1-phosphate, uridine disphosphoglucose, and NADP. In the presence of galactose-1-phosphateuridyl transferase, a sequence of enzyme reactions proceed with generation of NADPH which is detected by fluorescence. Deficient specimens will exhibit limited or an absence of fluorescence indicating a potential medical emergency. A confirmatory Galactose-1-Phosphate Uridyltransferase (GALT) test on whole blood should be performed as soon as possible for differential diagnosis.

The enzyme (Beutler assay) is prone to damage if the sample is delayed in the mail or exposed to high temperatures.

## Screening Practice Considerations

The Beutler assay test should be abnormal in all severe (classical) galactosemic infants even if the specimen is collected before lactose is ingested unless the infant has been transfused. **Always obtain a newborn screening specimen before any transfusion.** The enzyme (Beutler assay) is prone to damage if the sample is delayed in the mail or exposed to high temperatures.

Galactosemia should be considered in any infant with non-glucose reducing substances in the urine. NOTE: Galactose reacts with "Clinitest" and with most blood "glucose" methods such as Somogyi-Nelson, etc., which measure total blood sugars (but not with glucose oxidase methods, i.e., Clinistix).

## Actions to be Taken When Newborn Screening Test is Abnormal

If the newborn screening test is abnormal, milk formula and breastfeeding should be stopped until confirmatory testing is completed. The baby should be immediately examined. Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screens is present. These situations can include early specimen collection, prematurity, heat-damaged specimen, hyperalimentation, or antibiotic therapy. The presence of any of these does not exclude the possibility of disease

Infants with a positive (abnormal) test for galactosemia should be placed on a formula without galactose and lactose until confirmatory testing is complete. Recommended formulas include Isomil and Prosobee, in the powdered form. The concentrated and ready-to-feed formulas of these brands contain more galactose due to carrageenan in the liquid.

Neocate and Elecare are also appropriate choices and have less galactose than the soy formulas. Currently they are not recommended over the soy formulas.

The lactose free versions of formulas, such as Similac Lactose-free or Enfamile Lactofree are <u>NOT APPROPRIATE</u>, as they contain some galactose.

## Treatment

If the newborn screening test is abnormal, milk formula and breastfeeding should be stopped until confirmatory testing is completed and the baby should be immediately examined. Consultation with a pediatric metabolic specialist should be made for confirmation and diagnosis.

The galactosemia syndromes are effectively treated by a rigid dietary exclusion of all galactose. Exclusion of milk and milk products alone does not constitute a galactose-restricted diet, as galactose is found in other foods as well. This galactose-free diet must be followed for life and requires close supervision and monitoring.

Recommended formulas include Isomil and Prosobee, in the powdered form. The concentrated and ready-to-feed formulas of these brands contain more galactose due to

carrageenan in the liquid. Neocate and Elecare are also appropriate choices and have less galactose than the soy formulas. Currently they are not recommended over the soy formulas.

The lactose free versions of formulas, such as Similac Lactose-free or Enfamile Lactofree are NOT APPROPRIATE, as they contain some galactose.

## Dietary Management of Galactosemia

The main goal of dietary management of galactosemia is to remove any foods containing galactose from the diet. Because milk and milk products are the most common food source of galactose, persons with galactosemia should avoid these foods. In the past, there was some controversy about how long a person with galactosemia should remain on a galactose-restricted diet. It is now recommended that persons with galactosemia should avoid eating foods with galactose throughout life.

- **Diet**
  Ideally, a person with galactosemia should have a blood gal-1-p level below 3 to 4 mg/100 ml. A galactose-restricted diet should keep blood gal-1-p at this level, while containing enough nutrients for normal body function. The diet allows most protein-containing foods other than milk and milk products. Fruits, vegetables, grains, breads, fats and sugars are acceptable, as long as they do not have ingredients that contain galactose. Some fruits and vegetables do contain small amounts of galactose. However, the form of galactose (bound galactose) found in fruits and vegetables is not usable by the body, and may not contribute to elevated blood gal-1-p. Recent research has shown that bound galactose may in fact be usable by the body, but further studies are needed to confirm this.[6]

- **Food Labels**
  Reading food labels is an essential component of managing galactosemia. As the young child transitions to table foods, parents must continue to read food labels to identify any ingredients which are unacceptable in the diet for galactosemia. The products to be avoided in processed foods are milk, casein, dry milk solids, lactose, curds and whey. The milk proteins casein and caseinate must be limited in the diet. They can provide large amounts of galactose if many foods or large amounts of any food containing casein are eaten. The following products may be used because they do not contain lactose: lactate, lactic acid, lactylates and calcium compounds. Food labels should be checked every time, since the ingredients in food products can change without notice. As the child matures, he or she can be involved in reading food labels as well and should become increasingly responsible for this task. [6]

- **Medicine**
  Lactose is often used as a filler or inactive ingredient in medicines and might not be listed on the package. The best way to ensure that a medication does not contain fillers with galactose is to ask a pharmacist. They should have access to information about medication ingredients. If possible, have a pharmacist be aware of what medication ingredients are unacceptable to you. This is the most effective way of avoiding galactose-containing medications.[6]

- **Dietary Supplements**
  Dietary supplements should be taken only when recommended by the physician or health care professional. Federal regulations require that these products be labeled for the percentage of US RDA nutrients; fillers or inactive ingredients are not listed. Because lactose may be used as a filler in some dietary supplements, it is important to check with a pharmacist to ensure a supplement does not contain any hidden sources of galactose.

  Milk and milk products are the usual dietary source of calcium. Because persons with galactosemia remove milk products from their diet, they need to add calcium back into their diet through supplements. All people with galactosemia should have a regular daily supplement of calcium either from a soy formula or tablets. Consult your doctor or nutritionist to find out how much calcium supplementation is right for you. [6]

**Some foods/ingredients containing galactose include:**

| | |
|---|---|
| Butter | Buttermilk and solids |
| Calcium caseinate | Casein |
| Nonfat milk | Cream |
| Dry milk and milk protein | Garbanzo beans |
| Hydrolyzed protein made from casein or whey | Ice cream |
| Lactalbumin (milk albuminate) | Lactose |
| Milk and milk solids | Milk chocolate |
| Nonfat dry milk & solids | Cheese |
| Organ meats (liver, heart, etc.) | Sherbet |
| Sodium caseinate | Sour cream |
| Whey and whey solids | Yogurt |
| Lactoglobulin | Margarine made with milk or soy |
| Dry beans and peas | Milk derivatives |
| Dried cheese | Calcium Caseinate |
| Tragacanth gum | Human Milk |

Even with continued dietary management, many individuals with galactosemia may see a decline in IQ, delay and deficient speech development, stunted growth, and infertility.

**Internet Resources**

Van Calcar, S. Galactosemia: Dietary Management. In Dietary Management Handbook [On-line]. Available: http://www.galactosemia.org/unallowed.htm

Maternal and Child Health Bureau. (1999). Galactosemia: An Overview. In Adult Metabolic Transition Project [On-line]. Available: http://depts.washington.edu/transmet/gal.html

Elsas II, L. J. (1999). Galactosemia. In Gene Clinics [On-line]. Available: http://www.geneclinics.com/profiles/galactosemia/

# Supplemental Newborn Screening

Through an agreement with Baylor University Medical Center in Dallas, Texas, the South Department of Health also offers supplemental newborn screening for more that 30 disorders such as MCAD (medium chain acyl CoA dehydrogenase deficiency) not mandated to be tested for in the state. When the state-mandated tests are performed, a sample of blood is taken by pricking the baby's heel. An additional small sample of blood can be collected at the same time as the required sample and is then dried on a piece of filter paper and sent to CLM along with the filter paper for the mandated tests. CLM will then forward the filter paper specimen to the Institute of Metabolic Disease Laboratory at Baylor University Medical Center for testing..

A consent form signed and dated by a parent or legal representative is required prior to performing supplemental newborn screening. Contact the state's designated central laboratory, CLM, at 1-800-522-2561 or 605-328-5464 for specific consent form information.

Supplemental newborn metabolic screening is performed on dried blood spots contained on filter paper cards by which amino acids, acylcarnitines, and other compounds in the blood spots are extracted, derivatized, and analyzed quantitatively by sensitive and specific tandem mass spectrometry. This screening process has the potential for detecting the following metabolic disorders** (as of September 2001):

1. Argininemia
2. Argininosuccinate Lyase Deficiency
3. Carnitine Palmitoyltransferase II Deficiency
4. Carnitine/Acylcarnitine Translocase Deficiency
5. Citrullinemia
6. Glutaric Aciduria Type I
7. Homocystinuria: Cystathionine Synthase Deficiency
8. 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency
9. Hyperammonemia, Hyperonithinemia, Homocitrullinuria Syndrome
10. Hypermethioninemia
11. Isobutryl-CoA Dehydrogenase Deficiency
12. Isovaleric Acidemia
13. Long-Chain Hydroxyacyl-CoA Dehyrogenase Deficiency
14. Malonic Aciduria
15. Maple Syrup Urine Disease
16. Medium-Chain Acyl-CoA Dehydrogenase Deficiency
17. 2-Methylbutyrl-CoA Dehydrogenase Deficiency
18. 3-Methylcrotonyl-CoA carboxylase Deficiency
19. Methylmalonic Acidemia
20. Mitochondrial Acetoacetyl-CoA Thiolase Deficiency
21. Multiple Acyl-CoA Dehydrogenase Deficiency
22. Nonketotic Hyperglycinemia
23. 5-Oxoprolinuria
24. Phenylketonuria

25. Propionic Acidemia
26. Short-Chain Acyl-CoA Dehydrogenase Deficiency
27. Trifunctional Protein Deficiency
28. Tyrosinemia Type I
29. Tyrosinemia Type II
30. Very Long-Chain Acyl-CoA Dehydrogenase Deficiency

** Although the aforementioned list of metabolic diseases is an accurate list of the diseases that are detectable through the screening processes being performed, under no circumstances can it be guaranteed that the screening process will for each patient tested detect the existence or non-existence of each of the aforementioned listed diseases. Like many screening processes, the screening process being conducted is a tool to be utilized by health care providers to assist them in attempting to detect the existence of a number of diseases whose detection is dependent upon a number of factors, some of which are outside the parameters of the Screening Services being performed.

--Baylor Institute of Metabolic Diseases

Supplemental newborn metabolic screening must be ordered by a physician. Parents who are interested in supplemental screening for their infant should request it of their doctor if the physician does not routinely order this screening. Physicians will be notified directly by the Central Laboratory if one of the disorders that is life threatening is detected, so that appropriate follow-up and education can be provided by the physician.

The following Web sites have information about supplemental newborn screening conditions:

http://www.fodsupport.org/mcad_fam.htm
MCAD: Medium Chain acyl CoA Dehydrogenase Information for Families

http://www.baylorhealth.com/newbornscreening/
Baylor University Medical Center Supplemental Newborn Screening

http://www.fodsupport.org/mcad.htm
MCAD: Medium Chain acyl CoA Dehydrogenase Information for Clinicians

http://www.geneclinics.org/profiles/mcad/details.html
University of Washington

# Resource Page

## Telephone Numbers

South Dakota Newborn Metabolic Screening Program (SDNMSP) ..... 1-605-773-3737
.....or 1-800-738-2301

SDNMSP Medical Consultant ..... 1-605-333-7188
Dr. Laura Keppen- Pediatric Endocrinology, Genetics & Metabolic Disease

Clinical Laboratories of the Midwest.....605- 328 -5464
.....or 1-800-LABCLM1 (1-800-522-2561)

## Website Address

SDNMSP Web page.....http://www.state.sd.us/doh/Famhlth/newborn.htm

### Newborn Screening Video

The First Step (1992; 20 min.;$190; order code LA4-A2-V). It can be ordered from NCCLS, 1-610-688-0100

### Wall Charts to Assist in Specimen Collection - Two full-color wall charts on specimen collection:

"Newborn Screening Blood Specimen Collection and Handling Procedure"
"Simple Spot Check" (invalid specimens and their causes) are available at no charge from:
Schleicher & Schuell
P.O. Box 2012
Keene, NH 03431
1-800-437-7003
603-357-7700 (FAX)

# Acknowledgements and References

The following people have provided review and comment for the South Dakota Newborn Metabolic Screening Practitioners' Manual.

Dr. Laura Keppen.....Medical Consultant ,SDNMSP
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Teri Christensen .....Nurse Consultant, SDNMSP, SD DOH
Terry Disburg .....Nurse Consultant, SDNMSP, SD DOH
Kayla Tinker..... Administrator, Office of Family Health, SD DOH
Nancy Hoyme.....CSHS Program Manager/MCH Coordinator, SD DOH
Barb Buhler .....Information Officer, SD DOH

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3. AAP Section on Endocrinology and Committee on Genetics, American Thyroid Association Committee on Public Health. "Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines". Pediatrics, 91, 6, June 1993, 1203-1209, 17 July 2001. Available: http://www.aap.org/policy/04407.html.

4. AAP Committee on Genetics. "Newborn Screening Fact Sheets". Pediatrics, 98, 3, September 1996, 473-501, 18 July 2001. Available: http://www.aap.org/policy/01565.html.

5. Van Calcar, S. "Galactosemia: Dietary Management". Dietary Management Handbook, Available: http://www.galactosemia.org/unallowed.htm.

6. Maternal and Child Health Bureau. "Galactosemia: An Overview". Adult Metabolic Transition Project, December 1999, 20 July 2001. Available: http://depts.washington.edu/transmet/gal.html.

7. Elsas II, L. J. "Galactosemia". Gene Clinics, February 2000, 20 July 2001. Available: http://www.geneclinics.com/profiles/galactosemia/.

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Available: http://thearc.org/faqs/pku.html.

9. Koch, R. K. "Issues in Newborn Screening for Phenylketonuria". American Family Physician, October 1999, 19 July 2001. Available: http://www.aafp.org/afp/991001ap/1462.html .

10. http://depts.washington.edu/transmet/The%20process/essential.htm#Diet .

11. http://www.cdc.gov/mmwr/preview/mmwrhtml/00000243.htm.

# Glossary of Terms and Acronyms

1. "Birth attendant" – a person licensed or certified by the state to provide maternity care and to deliver pregnant women;

2. "Central laboratory" – the department's designated laboratory;

3. "CH" – congenital hypothyroidism;

4. "Days of age" – the measure of the age of a newborn in 24-hour periods; i.e., a newborn is one day of age 24 hours following the hour of birth;

5. "Department" – the South Dakota Department of Health;

6. "Designated laboratory" – a laboratory or laboratories authorized by the department pursuant to 44:19:02:03.01 to perform newborn screening services for the residents of South Dakota;

7. "Discharge" – the release of a newborn from the care of an institution of hospital to the parents or into the community;

8. "Enzyme" – a complex organic compound secreted by living cells which causes or accelerates chemical reactions or changes in a substrate;

9. "EVRSS" – the Electronic Vital Records and Screening System that links newborn metabolic screening and newborn hearing screening with each infants birth certificate.

10. "FT4" – free thyroxine

11. "Galactosemia" – a metabolic disease indicated by the presence of an excessive amount of galactose in the blood due to a deficiency of galactose-1-phosphate uridyl transferase;

12. "Hypothyroidism" – a disease indicated by low level of thyroxine in the serum of the newborn;

13. "Inadequate specimen" – a newborn's blood specimen which is not suitable in quality or quantity for performing newborn screening for one or more of the disorders requested;

14. "Indeterminate result" - test results do not adhere to present criteria established for interpretation of a normal or an abnormal result. Additional testing usually recommended;

15. “Initial abnormal specimen” – a newborn’s blood specimen which is defined as positive for reporting purposes;

16. “Initial specimen” – the first screening specimen collected subsequent to birth;

17. “Initial test” – the first valid screening test or combination of tests of a newborn for each disorder;

18. “Metabolic disease” – a malfunction in the processes that convert compounds to protoplasm, energy, and waste;

19. “Newborn” – an infant 28 days of age or under;

20. “Newborn’s physician” – the physician responsible for the care of a newborn after discharge from the hospital;

21. “Phe” – blood phenylalanine;

22. “PKU” “phenylketonuria” – a metabolic disease indicated by an excessive amount of phenylalanine in the serum of the newborn;

23. “Repeat specimen” – a specimen collected from a newborn because a previously collected specimen was either inadequate or the rest results were inconclusive or abnormal;

24. “Repeat test” – a test repeated because the previous specimen or test results were inadequate, test results were not complete, or the rest results were abnormal;

25. “T4” – Symbol for thyroxine;

26. “TPN” – Total parenteral nutrition or hyperalimentation;

27. “Transfer” – the release of a newborn from the care of one institution or hospital to the care of another institution or hospital;

28. “TSH” – thyroid stimulating hormone;

29. “Unacceptable or unsatisfactory specimen” – a newborn’s blood specimen that is not suitable in quality or quantity for performing newborn screening for one or more of the disorders covered by this manual.

## INADEQUATE OR INACCURATE IDENTIFYING INFORMATION

### Laboratory Specimen Requisition

- Complete **all** requested information on the requisition. Incomplete or inaccurate information will affect the turnaround time.

- **Test results are dependent on complete and accurate information**. For example, if the infant has been transfused but the information on the requisition indicates "No transfusion", the interpretation of test results can be greatly affected.

- Print carefully, preferably using block letters, so information is legible.

- This information is vital for identification and location of infants for follow-up of abnormal test results; it must be accurate, legible, and complete.

- Follow-up often requires **linking the first specimen result with a repeat or second specimen** submitted for testing. Key information used is: 1) the baby's last name, 2) mother's maiden and first name, and 3) baby's date of birth. Such linking may not occur if information is recorded erroneously on the requisition, **or** if the baby's last name has changed since the first specimen was submitted. **If the baby's last name has changed,** please write: "Baby's name was _____" in the " *Additional Comments"* section (lower left corner) of the requisition.

### Filter Paper Blood Collection Card

- Complete the required information on the blood collection card using a blue or black ball point pen only.

- Do not touch the filter paper blood collection circles while recording the information.

- Print carefully, preferably using block letters, so information is legible.

- Verify that the infant's name on the blood collection card is *identical* to the name on the requisition, If it is not, turnaround time of testing may be affected.

- Attach the requisition identification number (at lower right corner of test requisition) to the filter paper blood collection care in the area designated "Place Requisition Sticker Here." The requisition identification number must also be added to the Birth Certificate certified worksheet.

# SDNMSP BLOOD COLLECTION SUPPLIES

All newborn screening blood collection supplies are available from the Designated Laboratory (CLM) at no charge by calling:

**Supplies**…….1-605-328-5466 or 1-800-522-2561, ext. 8-5466

**Filter Paper Blood Collection Card**

Store filter paper collection cards in original wrapping or plastic ziplock bag at room temperature and stacked on their sides to avoid compressing the filter paper. The collection cards outdate in two years.

### SDNMSP Laboratory Screening Requisition

Some facilities have a computer interface with CLM, such as the ClinScan or an interface via NDR. Each time a newborn screening request is entered, the computer prompts the operator to enter the same required information as requested on the "paper" Newborn Screening Requisition. The computer generates the requisition with a unique identification number (a nine-character alpha/numeric field) and bar code labels for specimen identification.

Each requisition is preprinted with: 1*) a unique requisition number*, 2) the facility's CLM client number, and 3) the facility address information. After completion of the requested information, tri-fold the requisition, and place the requisition AND dried collection card in the mailing envelope provided. The client/facility may retain the second copy for its record. The top or "original" portion of the requisition must accompany the specimen. Please DO NOT separate the requisition copies and use them for two different infants; and DO NOT submit a photocopy of the requisition. Such actions will significantly delay testing.

With implementation of the EVRSS system, it is important that all hospitals performing newborn screening prior to hospital discharge include the unique identification number on the Birth Certificate Certifier's Worksheet. Each birth facility should have a process in place for assuring this occurs.

### Instructions for Proper Use of SDNMSP Supplies

Instructions are contained in this manual. To obtain a separate copy of instructions, please request it from the Supplies Department.

### Preaddressed Return Envelopes

Two types of #10 paper envelopes are available:

1) a business reply postage-paid envelope for mailing
2) a courier delivery envelope for clients/facilities serviced by a CLM courier

Place each infant screening in **a separate envelope** and seal. Do not use plastic or plasticene envelopes, or place envelopes in a zip lock plastic bag. Humidity and moisture are detrimental to the stability of dried blood spot specimens and can affect results.

# South Dakota Newborn Metabolic Statutes

34-24-17. Screening of newborn infants for metabolic disease. All infants born in the state of South Dakota shall be screened for metabolic disease. This screening shall be as prescribed by the state department of health.

34-24-18. Phenylketonuria, hypothyroidism and galactosemia testing in newborn. The tests for detecting metabolic disorders of the newborn infant, as prescribed by the department of health, shall include, but not be limited to, the testing for excessive phenylalanine in the serum of the newborn, for hypothyroidism and for elevated blood galactose in the newborn.

34-24-19. Phenylketonuria, hypothyroidism or galactosemia tests when facilities not available. If facilities are not available for the screening of newborn infants for the Phenylketonuria syndrome, for hypothyroidism or for galactosemia, the department of health shall arrange for testing through the director of laboratories.

34-24-20. Phenylketonuria, hypothyroidism and galactosemia tests provided by department for newborn not tested. If the required report to the department of health shows that the newborn infant was not tested for Phenylketonuria, for hypothyroidism or for galactosemia, the department may arrange for the infant to be tested.

34-24-21. Procedures prescribed after positive Phenylketonuria, hypothyroidism or galactosemia tests. If a screening test indicates a newborn infant may be afflicted with the Phenylketonuria syndrome, hypothyroidism or galactosemia, the department of health shall prescribe the procedures to be followed in order to determine if the syndrome is actually present.

34-24-22. Testing for other metabolic diseases. When tests for detecting a metabolic disease other than Phenylketonuria, hypothyroidism and galactosemia are perfected, the department of health may require that tests for the syndrome or syndromes be made and reported to the health department.

34-24-23. Reports to department on metabolic disease tests -- Forms. Results of such tests for metabolic disorders in infants, as prescribed by the department of health, shall be sent to the department on forms to be prescribed and furnished by the department to all physicians, public health nurses and hospitals.

34-24-24. Follow-up on children with metabolic disease. It shall be the responsibility of the department of health to follow the development of all children carrying the syndrome of any metabolic disease to ensure that those persons responsible for the care of the child are fully informed of accepted medical procedures for the detection, prevention, and treatment of such condition.

34-24-25. Rules and regulations. The department of health is authorized to promulgate and enforce rules and regulations to aid in implementing the provisions of § 34-24-16 to 34-24-24, inclusive.

# SDNMSP Administrative Rules

## ARTICLE 44:19

## NEWBORN SCREENING



## CHAPTER 44:19:01

## DEFINITIONS



**44:19:01:01. Definitions.** Words used in this article mean:

(1) "Birth attendant," a person licensed or certified by the state under SDCL title 36 to provide maternity care and to deliver pregnant women;

(2) "Days of age," the measurement of the age of a newborn in 24-hour periods; i.e., a newborn is one day of age 24 hours following the hour of birth;

(3) "Department," the South Dakota Department of Health;

(4) "Designated laboratory," a laboratory or laboratories authorized by the department pursuant to § 44:19:02:03.01 to perform newborn screening services for the residents of South Dakota;

(5) "Discharge," the release of a newborn from the care of an institution or hospital to the parents or into the community;

(6) "Enzyme," a complex organic compound secreted by living cells which causes or accelerates chemical reactions or changes in a substrate;

(7) "Galactosemia," a metabolic disease indicated by the presence of an excessive amount of galactose in the blood due to a deficiency of galactose-1-phosphate uridyl transferase;

(8) "Hypothyroidism," a metabolic disease indicated by a low level of thyroxine in the serum of the newborn;

(9) "Inadequate specimen," a newborn's blood specimen which is not suitable in quality or quantity for performing newborn screening for one or more of the disorders covered by this article;

(10) "Initial abnormal specimen," a newborn's blood specimen which is defined as positive for reporting purposes;

(11) "Initial specimen," the first metabolic screening specimen collected subsequent to birth;

(12) "Initial test," the first valid metabolic screening test or combination of tests of a newborn for each disorder;

(13) "Metabolic disease," a malfunction in the processes that convert compounds to protoplasm, energy, and waste;

(14) "Newborn," an infant 28 days of age or under;

(15) "Newborn's physician," the physician responsible for the care of a newborn after discharge from the hospital;

(16) "PKU," "phenylketonuria," a metabolic disease indicated by an excessive amount of phenylalanine in the serum of the newborn;

(17) "Repeat specimen," a specimen collected from a newborn because a previously collected specimen was either inadequate or the test results were inconclusive or abnormal;

(18) "Repeat test," a test repeated because the previous specimen or test results were inadequate, test results were not complete, or the test results were abnormal;

(19) "Secretary," the secretary of the department of health;

(20) "T4," symbol for thyroxine;

(21) "Transfer," the release of a newborn from the care of one institution or hospital to the care of another institution or hospital; and

(22) "TSH," thyroid stimulating hormone.

**Source:** 12 SDR 167, effective April 20, 1986; 15 SDR 59, effective October 19, 1988; 18 SDR 67, effective October 16, 1991; 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-23.

**44:19:01:02. Transferred to § 44:19:02:03.**

**44:19:01:03. Deadlines for reporting test results.** Repealed.

**Source:** 12 SDR 167, effective April 20, 1986; repealed, 15 SDR 59, effective October 19, 1988.

## CHAPTER 44:19:02

## NEWBORN SCREENING LABORATORY

Section



**44:19:02:01. Newborn screening laboratory test requisition.** Repealed.

**Source:** 15 SDR 59, effective October 19, 1988; repealed, 23 SDR 91, effective December 9, 1996.

**44:19:02:02. Standards for laboratory operation.** Repealed.

**Source:** 15 SDR 59, effective October 19, 1988; 18 SDR 67, effective October 16, 1991; repealed, 23 SDR 91, effective December 9, 1996.

**44:19:02:03. Reporting requirements.** Repealed.

**Source:** 12 SDR 167, effective April 20, 1986; transferred from § 44:19:01:02, 15 SDR 59, effective October 19, 1988; 18 SDR 67, effective October 16, 1991; repealed, 23 SDR 91, effective December 9, 1996.

**44:19:02:03.01. Designation of laboratories.** In accordance with criteria in § 44:19:02:03.02 the department shall designate the laboratories that are authorized to perform newborn screening services for the residents of South Dakota. The number of laboratories to be designated at any one time is at the discretion of the secretary.

**Source:** 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-25.

**44:19:02:03.02. Criteria for designation of laboratories.** The department shall use the following criteria in designating laboratories to conduct newborn screening tests:

(1) Professional qualifications necessary for satisfactory performance of the required services;
(2) Demonstrated experience and technical expertise;
(3) Demonstrated capacity to accomplish work in the required time and maintain a continuity of services;
(4) Past performance on similar contracts with publicly or privately funded programs in terms of cost control, quality of work, and compliance with performance schedules;
(5) Proposed fee to be charged per specimen for newborn screening; and
(6) Any other criteria as deemed appropriate by the secretary.

**Source:** 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-25.

**44:19:02:04. Public notice of designated laboratories.** The department shall publish the names and addresses of the designated laboratories authorized to conduct newborn screening tests.

**Source:** 15 SDR 59, effective October 19, 1988; 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-25.

**44:19:02:05. Responsibilities of parents, hospitals, physicians, and other health professionals.** The parents, guardian, or custodian of each infant is responsible for having blood tests for metabolic diseases performed within the first seven days of an infant's life, preferably between the third and fifth day of life.

The attending physician, other health professional, hospital, or public health facility shall notify the parents, guardian, or custodian of each infant of the responsibility to have the newborn screening tests performed.

If a parent, guardian, or custodian refuses consent for newborn screening to be completed for any infant, the attending physician, other health professional, hospital, or public health facility shall notify legal counsel for the department by telephone at 773-3361 within 24 hours after the refusal.

**Source:** 18 SDR 67, effective October 16, 1991; 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-17, 34-24-23, 34-24-24.

## CHAPTER 44:19:03

## TIME SEQUENCE FOR TESTING

Section


**44:19:03:01. Specimen submission to designated laboratory.** Specimens must be submitted to a designated laboratory. Only filter paper specimens may be submitted for newborn screening.

**Source:** 15 SDR 59, effective October 19, 1988; 18 SDR 67, effective October 16, 1991; 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-18.

**44:19:03:02. Collection of filter paper specimens.** Filter paper specimens for submission to designated laboratories must be collected as follows:

(1) A filter paper specimen must be collected from each newborn infant on or before the day of discharge by the institution or hospital where initial newborn care was provided regardless of feeding history or antibiotics being given;

(2) Newborns discharged before 24 hours of age may have a repeat specimen obtained within two weeks;

(3) Filter paper specimens must be obtained from premature newborns on the day of discharge or on the seventh day of age if nursery stay is prolonged beyond six days;

(4) Filter paper specimens must be obtained from newborns undergoing exchange transfusion prior to the exchange transfusion. A repeat specimen must be obtained at the time of discharge;

(5) The receiving institution must obtain filter paper specimens from newborns transferred within the first 48 hours of life;

(6) The institution initiating the transfer must obtain blood specimens from newborns transferred after the first 48 hours of life; and

(7) If a birth occurs that is not attended by a birth attendant, the local birth registrar shall inform the parent or guardian of the need for a blood test for metabolic diseases when a certificate of birth is filed. The registrar shall inform the parent or guardian where the blood sample may be drawn or refer them to the local community health nurse.

The submitted specimen must be sufficient to allow a repeat test or a TSH and must be retained by the designated laboratory until the laboratory or physician determines that those tests are unnecessary.

The department shall direct the community health nurse or a designee to act to fulfill these requirements as necessary to ensure submission of a specimen that meets the requirements of this section.

**Source:** 15 SDR 59, effective October 19, 1988; 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-18.

## CHAPTER 44:19:04

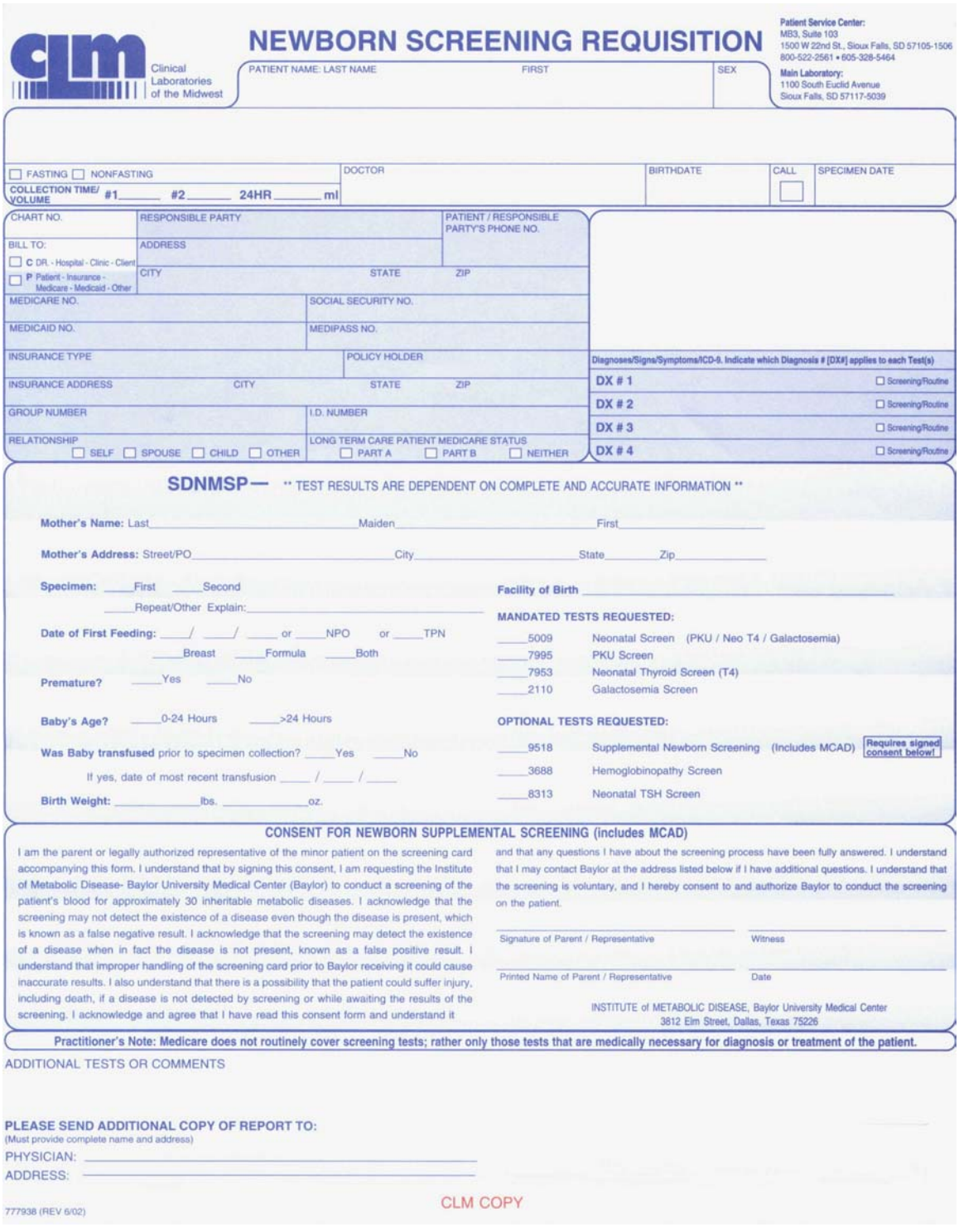
## CONSULTATION

Section


**44:19:04:01. Consultation services.** The department shall contract with a consulting physician to provide interpretation of test results and consultation to the attending physician on request.

**Source:** 15 SDR 59, effective October 19, 1988; 23 SDR 91, effective December 9, 1996.
**General Authority:** SDCL 34-24-25.
**Law Implemented:** SDCL 34-24-21, 34-24-24.

# APPENDIX A



CLM Clinical Laboratories of the Midwest

## NEWBORN SCREENING REQUISITION

Patient Service Center:
MB3, Suite 103
1500 W 22nd St., Sioux Falls, SD 57105-1506
800-522-2561 • 605-328-5464

Main Laboratory:
1100 South Euclid Avenue
Sioux Falls, SD 57117-5039

PATIENT NAME: LAST NAME | FIRST | SEX

☐ FASTING ☐ NONFASTING
COLLECTION TIME/ VOLUME #1_____ #2_____ 24HR_____ ml

DOCTOR | BIRTHDATE | CALL ☐ | SPECIMEN DATE

CHART NO. | RESPONSIBLE PARTY | PATIENT / RESPONSIBLE PARTY'S PHONE NO.

BILL TO:
☐ C DR. - Hospital - Clinic - Client
☐ P Patient - Insurance - Medicare - Medicaid - Other

ADDRESS
CITY | STATE | ZIP

MEDICARE NO. | SOCIAL SECURITY NO.

MEDICAID NO. | MEDIPASS NO.

INSURANCE TYPE | POLICY HOLDER

INSURANCE ADDRESS | CITY | STATE | ZIP

GROUP NUMBER | I.D. NUMBER

RELATIONSHIP ☐ SELF ☐ SPOUSE ☐ CHILD ☐ OTHER

LONG TERM CARE PATIENT MEDICARE STATUS ☐ PART A ☐ PART B ☐ NEITHER

Diagnoses/Signs/Symptoms/ICD-9. Indicate which Diagnosis # [DX#] applies to each Test(s)

DX # 1 ☐ Screening/Routine
DX # 2 ☐ Screening/Routine
DX # 3 ☐ Screening/Routine
DX # 4 ☐ Screening/Routine

### SDNMSP— ** TEST RESULTS ARE DEPENDENT ON COMPLETE AND ACCURATE INFORMATION **

**Mother's Name:** Last_____ Maiden_____ First_____

**Mother's Address:** Street/PO_____ City_____ State_____ Zip_____

**Specimen:** _____First _____Second
_____Repeat/Other Explain:_____

**Date of First Feeding:** _____/ _____/ _____ or _____NPO or _____TPN
_____Breast _____Formula _____Both

**Premature?** _____Yes _____No

**Baby's Age?** _____0-24 Hours _____>24 Hours

**Was Baby transfused** prior to specimen collection? _____Yes _____No
If yes, date of most recent transfusion _____ / _____ / _____

**Birth Weight:** _____lbs. _____oz.

**Facility of Birth** _____

**MANDATED TESTS REQUESTED:**

_____5009 Neonatal Screen (PKU / Neo T4 / Galactosemia)
_____7995 PKU Screen
_____7953 Neonatal Thyroid Screen (T4)
_____2110 Galactosemia Screen

**OPTIONAL TESTS REQUESTED:**

_____9518 Supplemental Newborn Screening (Includes MCAD) Requires signed consent below!
_____3688 Hemoglobinopathy Screen
_____8313 Neonatal TSH Screen

### CONSENT FOR NEWBORN SUPPLEMENTAL SCREENING (includes MCAD)

I am the parent or legally authorized representative of the minor patient on the screening card accompanying this form. I understand that by signing this consent, I am requesting the Institute of Metabolic Disease- Baylor University Medical Center (Baylor) to conduct a screening of the patient's blood for approximately 30 inheritable metabolic diseases. I acknowledge that the screening may not detect the existence of a disease even though the disease is present, which is known as a false negative result. I acknowledge that the screening may detect the existence of a disease when in fact the disease is not present, known as a false positive result. I understand that improper handling of the screening card prior to Baylor receiving it could cause inaccurate results. I also understand that there is a possibility that the patient could suffer injury, including death, if a disease is not detected by screening or while awaiting the results of the screening. I acknowledge and agree that I have read this consent form and understand it and that any questions I have about the screening process have been fully answered. I understand that I may contact Baylor at the address listed below if I have additional questions. I understand that the screening is voluntary, and I hereby consent to and authorize Baylor to conduct the screening on the patient.

Signature of Parent / Representative | Witness

Printed Name of Parent / Representative | Date

INSTITUTE of METABOLIC DISEASE, Baylor University Medical Center
3812 Elm Street, Dallas, Texas 75226

**Practitioner's Note: Medicare does not routinely cover screening tests; rather only those tests that are medically necessary for diagnosis or treatment of the patient.**

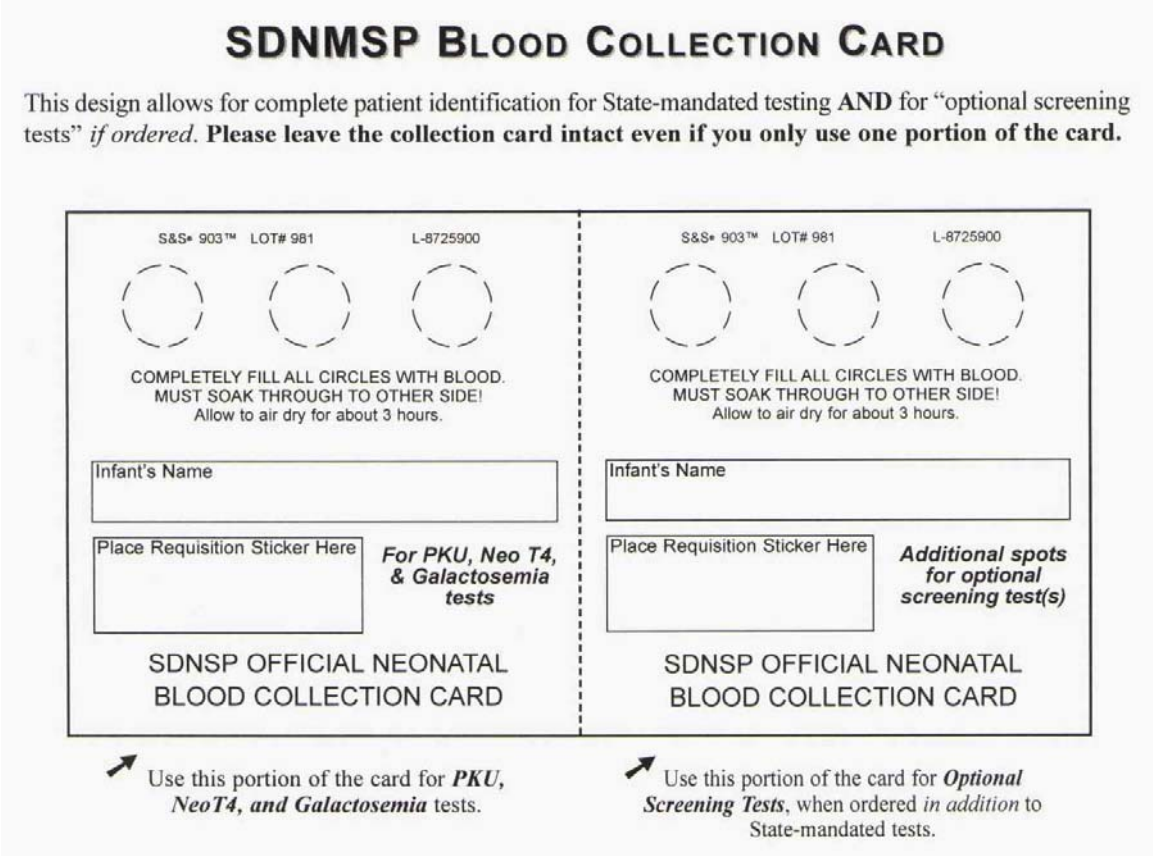
ADDITIONAL TESTS OR COMMENTS

**PLEASE SEND ADDITIONAL COPY OF REPORT TO:**
(Must provide complete name and address)
PHYSICIAN: _____
ADDRESS: _____

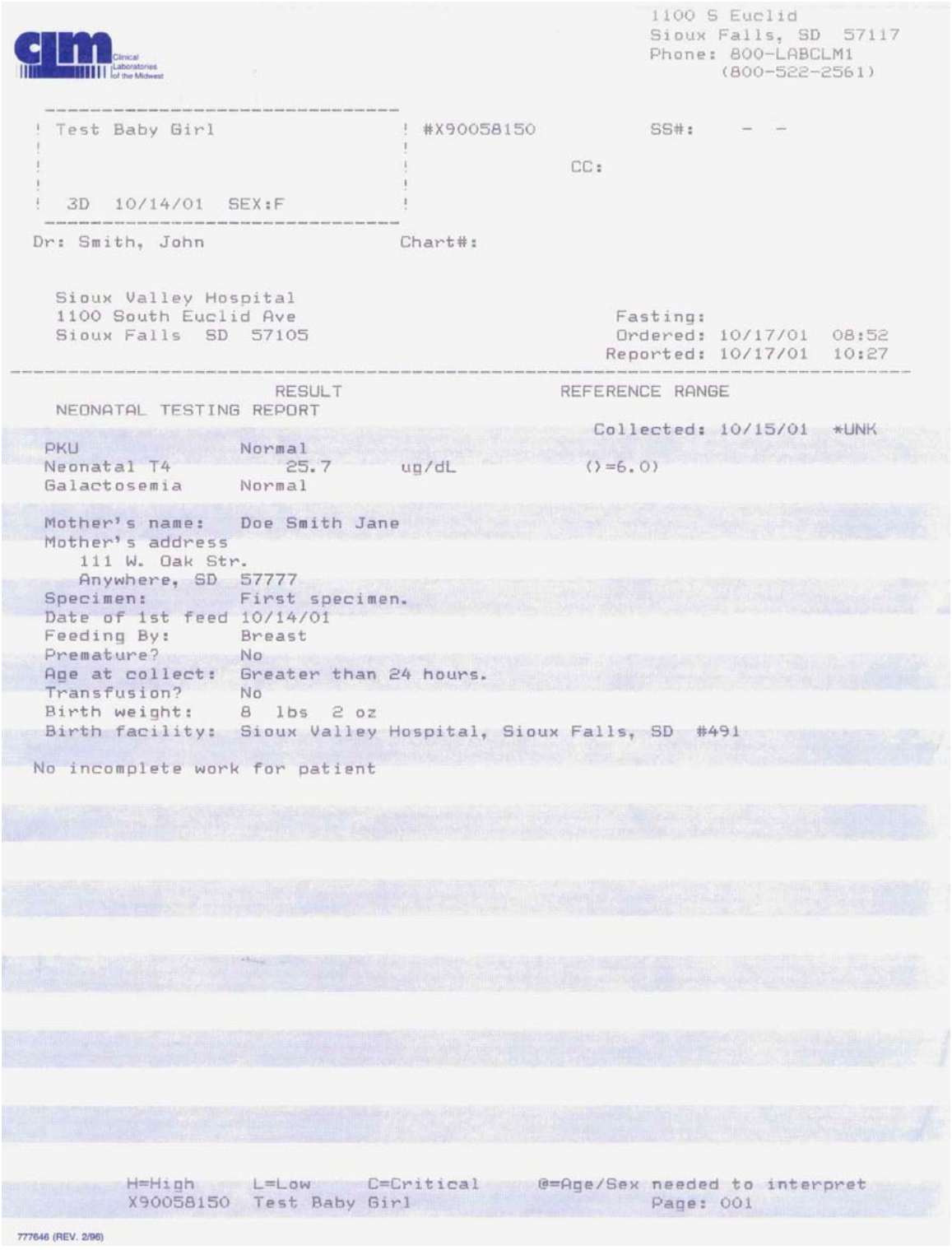
777938 (REV 6/02)

CLM COPY

**APPENDIX B**


SDNMSP BLOOD COLLECTION CARD
This design allows for complete patient identification for State-mandated testing AND for "optional screening tests" *if ordered*. **Please leave the collection card intact even if you only use one portion of the card.**
S&S• 903™ LOT# 981 L-8725900
COMPLETELY FILL ALL CIRCLES WITH BLOOD.
MUST SOAK THROUGH TO OTHER SIDE!
Allow to air dry for about 3 hours.
Infant's Name
Place Requisition Sticker Here
For PKU, Neo T4, & Galactosemia tests
SDNSP OFFICIAL NEONATAL BLOOD COLLECTION CARD
Use this portion of the card for PKU, NeoT4, and Galactosemia tests.
S&S• 903™ LOT# 981 L-8725900
COMPLETELY FILL ALL CIRCLES WITH BLOOD.
MUST SOAK THROUGH TO OTHER SIDE!
Allow to air dry for about 3 hours.
Infant's Name
Place Requisition Sticker Here
Additional spots for optional screening test(s)
SDNSP OFFICIAL NEONATAL BLOOD COLLECTION CARD
Use this portion of the card for Optional Screening Tests, when ordered in addition to State-mandated tests.

# APPENDIX C



CLM Clinical Laboratories of the Midwest

1100 S Euclid
Sioux Falls, SD 57117
Phone: 800-LABCLM1
(800-522-2561)

| Test Baby Girl | #X90058150 | SS#: - - |
|---|---|---|
| | CC: | |
| 3D 10/14/01 SEX:F | | |

Dr: Smith, John  Chart#:

Sioux Valley Hospital
1100 South Euclid Ave
Sioux Falls SD 57105

Fasting:
Ordered: 10/17/01 08:52
Reported: 10/17/01 10:27

NEONATAL TESTING REPORT

| | RESULT | | REFERENCE RANGE |
|---|---|---|---|
| | | | Collected: 10/15/01 *UNK |
| PKU | Normal | | |
| Neonatal T4 | 25.7 | ug/dL | ()=6.0) |
| Galactosemia | Normal | | |

Mother's name: Doe Smith Jane
Mother's address
111 W. Oak Str.
Anywhere, SD 57777
Specimen: First specimen.
Date of 1st feed 10/14/01
Feeding By: Breast
Premature? No
Age at collect: Greater than 24 hours.
Transfusion? No
Birth weight: 8 lbs 2 oz
Birth facility: Sioux Valley Hospital, Sioux Falls, SD #491

No incomplete work for patient

H=High L=Low C=Critical @=Age/Sex needed to interpret
X90058150 Test Baby Girl Page: 001

777646 (REV. 2/96)